Exhibit 3

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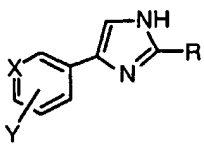
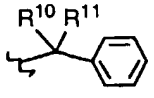
(54) Title: SUBSTITUTED IMIDAZOLE NEUROPEPTIDE Y Y5 RECEPTOR ANTAGONISTS



(I)



(A)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, wherein X is =CH- or =N-; Y is H, halogen, trihaloalkyl, alkyl, alkenyl, cycloalkyl, cycloalkyl, SH, -S-alkyl, or -CN. R is alkyl, $-CF_3$, cycloalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, heteroarylalky or adamantyl, or optionally substituted phenyl, phenoxyalkyl, phenylthioalkyl, pyridyl, thienyl, thiazolyl, pyrazinyl, 1,2,5,6-tetrahydropyridine or formula (A), wherein R_{10} and R_{11} are hydrogen, alkyl or together form a cycloalkyl, are disclosed, as well as pharmaceutical compositions and methods of using said compounds in the treatment of eating disorders and diabetes.

SUBSTITUTED IMIDAZOLE NEUROPEPTIDE Y Y5 RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

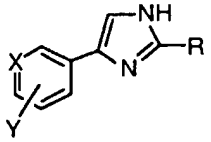
The present invention relates to selective 4-(phenyl or pyridyl)-imidazole derivative neuropeptide Y Y5 receptor antagonists useful in the treatment of eating disorders, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds.

Neuropeptide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies in animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis. Therefore compounds that antagonize neuropeptide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia, and diabetes.

Substituted imidazoles are used in various pharmaceutical and non-pharmaceutical applications. WO 99/01128 discloses substituted diarylimidazoles as NPY Y5 receptor antagonists.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by the structural formula I:



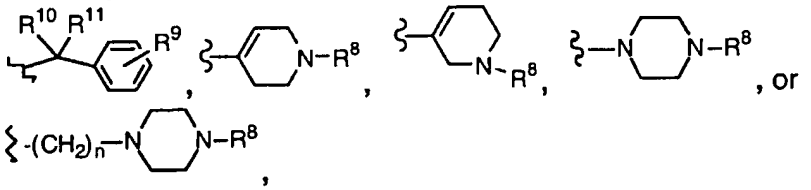
I

or a pharmaceutically acceptable salt, solvate or N-oxide thereof, wherein

X is =CH- or =N-;

Y is 1 to 3 substituents independently selected from the group consisting of H, halogen, trihaloalkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_7-cycloalkyl, C_1-C_6 alkyl substituted by C_3-C_7-cycloalkyl,-OH, -O(C_1-C_6)alkyl, -SH, -S(C_1-C_6)alkyl, or –CN.

R is R^1-phenyl, R^1-pyridyl, adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6alkyl, C_3-C_7-cycloalkyl, or heterocycloalkyl selected from the group consisting of 4 to 6 membered rings comprising 3 to 5 carbon ring members and 1 to 3 ring members selected from the group consisting of –NR^8-, -O- and -S-, heterocycloalkyl(C_1-C_6)alkyl wherein heterocycloalkyl is as defined above, heteroaryl(C_1-C_6)alkyl,



provided that when R is R^1-phenyl, R^1-pyridyl, adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6alkyl, or C_3-C_7-cycloalkyl, Y is 3-CF_3;

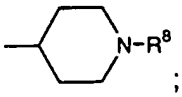
n is 0, 1, 2 or 3;

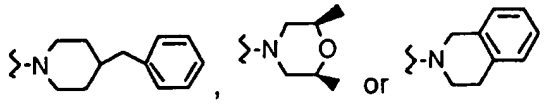
R^1 is 1-3 substituents independently selected from the group consisting of hydroxy(C_1-C_6)alkyl; NO_2; -CHO, -C(O)O(C_1-C_6)alkyl; -C(O)NR^4R^5; -$(CH_2)_p$$NR^4R^5$; -$(CH_2)_p$$NR^4R^6$; -$NR^4SO_2R^7$; -NHCOH; -$NR^4COR^5$; -NHC(O)$NR^4R^5$; aryl; and heteroaryl;

p is 0, 1, 2 or 3;

R^4 is hydrogen or C_1-C_6 alkyl;

R^5 is C_1-C_6 alkyl, aryl or heteroaryl; provided R^4 and R^5 are not both C_1-C_6 alkyl, and provided that when R^4 is hydrogen, R^5 is not C_1-C_6 alkyl; or R^4 and R^5 together are C_3-C_6 alkylene and together with the nitrogen to which they are attached form a 4-7 membered ring; or R^4 and R^5, together with the nitrogen to which they are attached, form a 5, 6 or 7-membered ring, wherein 1 or 2 ring members are independently selected from the group consisting of -O-, -S- and –NR^{12}-;

R^6 is C_3-C_7 cycloalkyl, benzyl, diphenylmethyl or  ; or R^4 and R^6, together with the nitrogen to which they are attached form a group of the formula

 ;

R^7 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, benzyl, aryl, or heteroaryl;

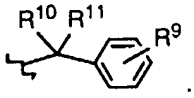
R^8 is hydrogen, C_1-C_6 alkyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_3-C_7 cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, -SO_2-R^7, aryl, heteroaryl, -$CONR^4R^5$ or -C(O)-O-(C_1-C_6)alkyl;

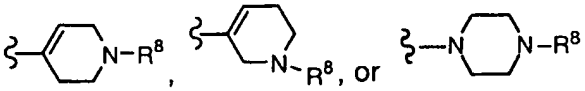
R^9 is 1 to 3 substituents independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogeno and -CF_3;

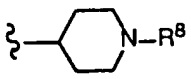
R^{10} and R^{11} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{10} and R^{11}, together with the carbon to which they are attached, form a C_3-C_7 ring; and

R^{12} is hydrogen, C_1-C_6 alkyl, -C(O)-(C_1-C_6 alkyl), -SO_2-R^7, R^9-phenyl, -$CONR^4R^5$, -C(O)-O-(C_1-C_6)alkyl, -CHO, C_3-C_7 cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, benzyl, benzoyl, -C(O)(C_3-C_7)cycloalkyl, -C(O)(C_1-C_6)alkylphenyl, pyridylmethyl, -C(O)pyridyl, -C(O)N(di-(C_1-C_6)-alkyl) or 4-tetrahydropyranyl.

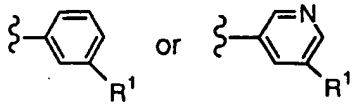
One group of preferred compounds is that wherein R is as defined above; R^1 is 1-3 substituents selected from the group consisting of hydroxy(C_1-C_6)alkyl, NO_2, -CHO, -C(O)O(C_1-C_6)alkyl, -$(CH_2)_pNR^4R^5$, -$(CH_2)_pNR^4R^6$, -$NR^4SO_2R^7$, -NHCOH, -$NHCOR^5$, -NR^4COR^5-, NHC(O)NR^4R^5, aryl and heteroaryl; and p is 0, 1 or 2.

Another group of preferred compounds is that wherein R is adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6 alkyl, C_3-C_7-cycloalkyl, heteroaryl-(C_1-C_6)alkyl, heterocycloalkyl-(C_1-C_6)alkyl, or  .

Another group of preferred compounds is that wherein R is heterocycloalkyl,  , wherein

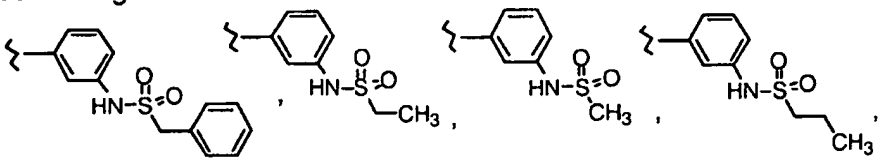
heterocycloalkyl is defined as  , and R8 is preferably C(O)-(C_1-C_6 alkyl), -C(O)-(C_3-C_7 cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, -SO_2-R^7, aryl, heteroaryl, and -$CONR^4R^5$.

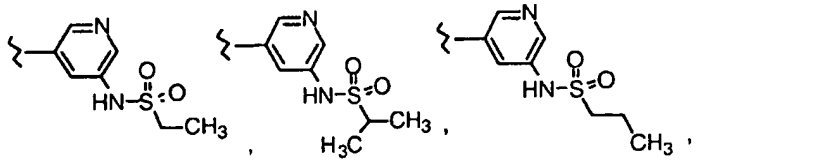
In another group of preferred compounds of formula I, R is R^1-phenyl or R^1-pyridyl of the formula

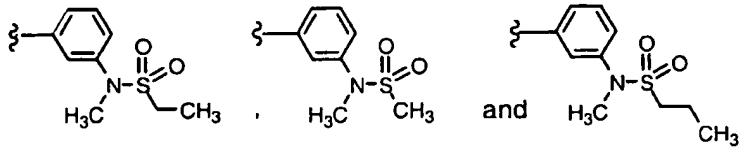


R^1 is preferably -$NR^4SO_2R^7$, wherein R^4 is H or straight or branched C_1-C_6 alkyl, and R^7 is straight or branched C_1-C_6 alkyl.

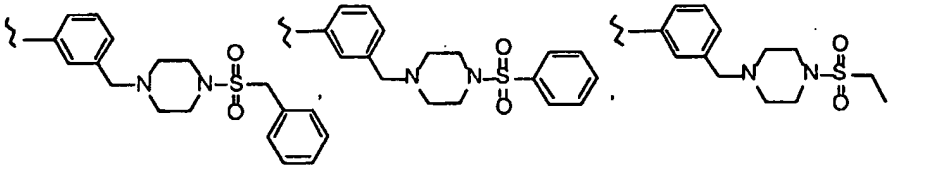
Preferred compounds of this invention include those of formula I wherein X is =CH-, Y is 3-CF_3, and R is selected from the group consisting of:

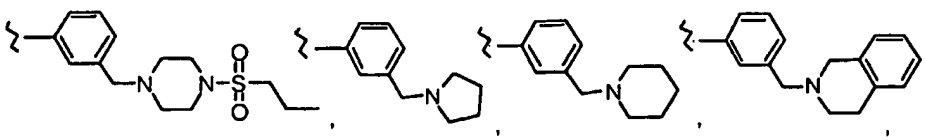


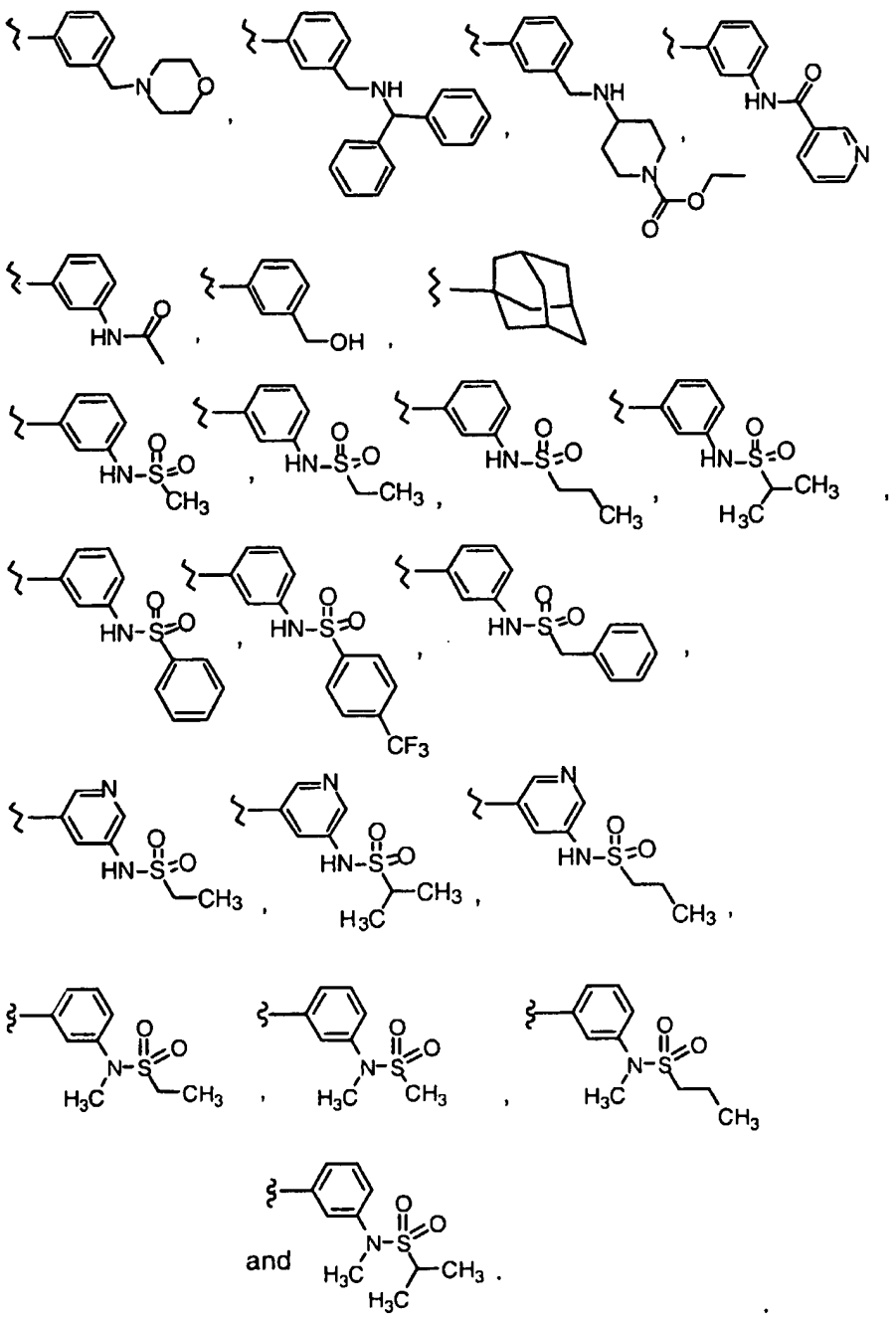




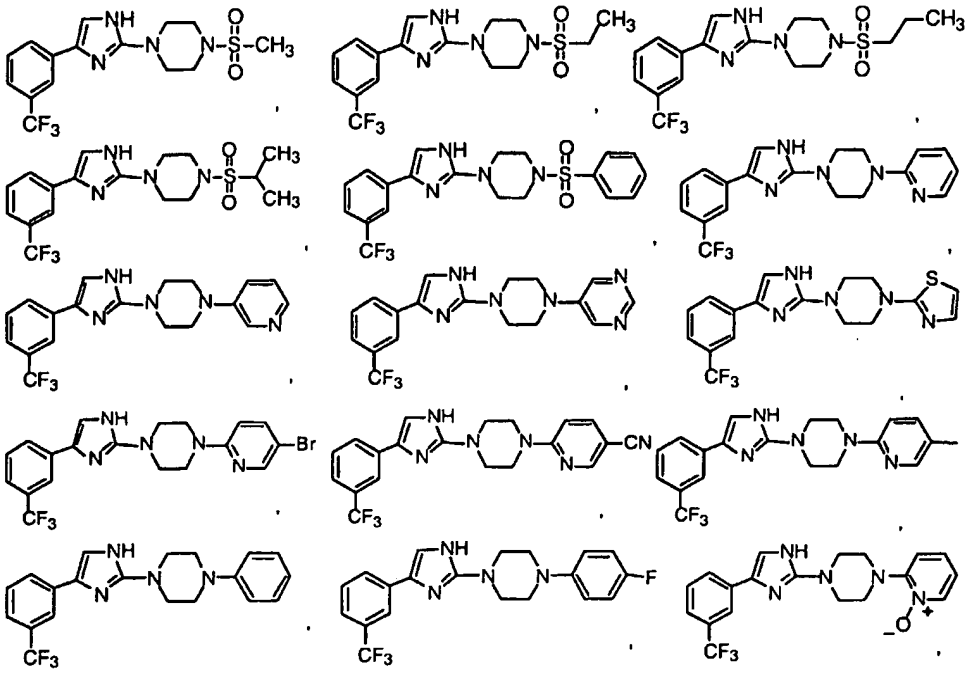
Another group of preferred compounds of this invention include those of formula 1 wherein X is =CH-, and R is selected from the group consisting of:



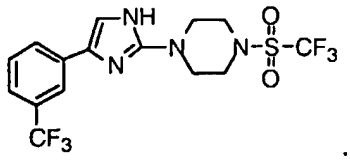




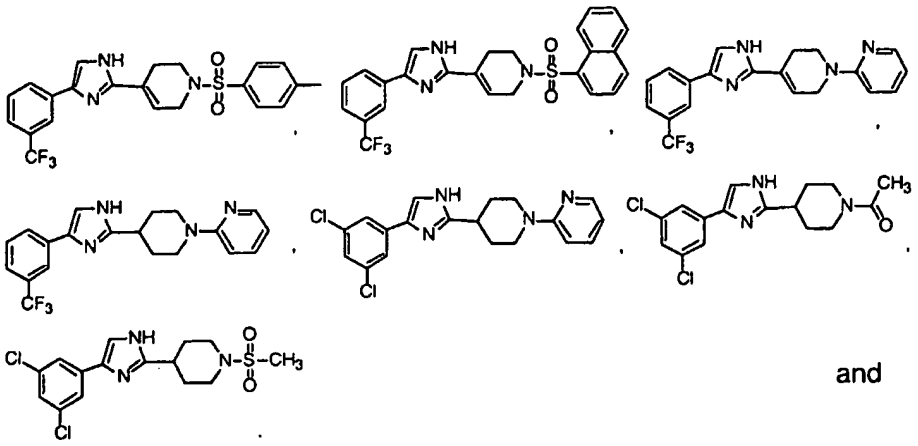
Still another group of preferred compounds of this invention include those selected from the group consisting of:



and



Yet one more group of preferred compounds of this invention include those selected from the group consisting of:



and

The present invention also relates to a method of treating eating disorders, such as obesity and hyperphagia, and diabetes comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I.

Another aspect of the invention is a pharmaceutical composition for treating eating disorders and diabetes which comprises a compound of formula I in combination with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

Except where stated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "alkoxy", etc.

Alkyl represents a straight or branched saturated hydrocarbon chain having the designated number of carbon atoms. If the number of carbon atoms is not specified, e.g., if the term lower alkyl is used, chain lengths of 1 to 6 carbons are intended.

Aryl-(including the aryl portion of arylalkyl and heteroarylalkyl)- represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with one or more (e.g., 1 to 3) of halo, alkyl,

hydroxy, alkoxy, phenoxy, CF_3, $-C(O)N(R^{18})_2$, $-SO_2R^{18}$, $-SO_2N(R^{18})_2$, amino, alkylamino, dialkylamino, $-COOR^{23}$ or $-NO_2$, wherein R^{18} represents H, alkyl, aryl, arylalkyl, heteroaryl or cycloalkyl and R^{23} represents alkyl or aryl;

Cycloalkyl represents a saturated carbocyclic ring having 3 to 7 carbon atoms.

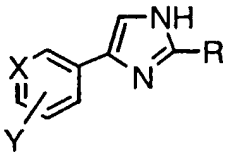
Halogeno represents fluoro, chloro, bromo or iodo.

As defined above, heterocycloalkyl represents 4 to 6 membered rings comprising 3 to 5 carbon ring members and 1 to 3 ring members selected from the group consisting of $-NR^{12}-$, -O- and -S-. Where a heterocycloalkyl ring comprises more than one heteroatom, no rings are formed where there are adjacent oxygen atoms, adjacent sulfur atoms, or three consecutive heteroatoms. Examples of heterocycloalkyl rings are piperazinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl and thiomorpholinyl.

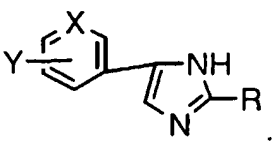
Heteroaryl means a 5 or 6-membered aromatic ring comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N=, provided that the rings do not include adjacent oxygen and/or sulfur atoms. Examples of heteroaryl groups are pyridyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazolyl. The heteroaryl rings are attached to the rest of the molecule through a ring carbon atom. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl. The substituted heteroaryl groups specifically identified in the definition of R, e.g. R^2-pyridyl and R^3-thiazolyl, can be substituted at any available ring carbon atom.

When a variable appears more than once in the structural formula, for example R^1, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

Compounds of the invention are tautomeric with respect to the 4- and 5-positions of the imidazoyl ring, i.e., the following structural formulae are equivalent:



and



N-oxides can form on a tertiary nitrogen present in an R substituent (e.g., R is 3-pyridyl *N*-oxide) or when X is = N-, in the Y substituted ring.

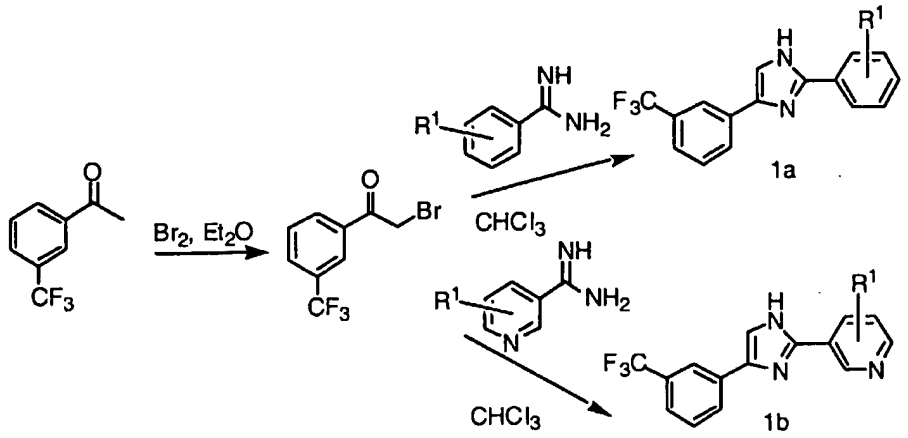
Compounds of formula I can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compounds of formula I may be produced by processes known to those skilled in the art as shown in the following reaction schemes and in the preparations and examples below.

Scheme 1:

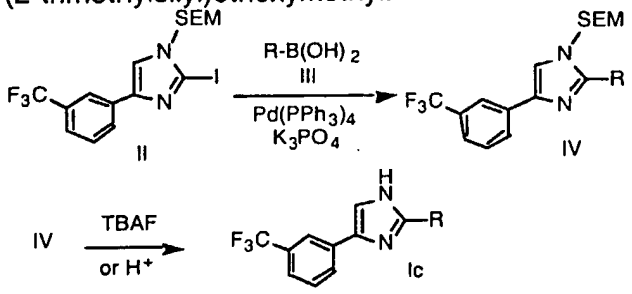
Compounds of formula 1a or 1b wherein X is -CH= and R is R^1-phenyl or R^1-pyridyl, respectively, can be prepared by the following procedure wherein the imidazolyl ring is formed during the reaction:



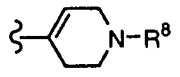
CF_3-substituted acetophenone is brominated, then reacted with a phenyl- or pyridyl-substituted amidine to obtain compounds of formula 1a or 1b. Compounds prepared by this method can be converted to other compounds of formula I by treating the R^1 substituent using methods well known in the art to obtain other R^1 substituents, e.g., an ester can be converted to an acid, an acid can be condensed with an amine, a nitro group can be reduced to an amine, and an amine can be sulfonated. When necessary, the NH moiety of the imidazolyl ring is protected with a group such as (2-trimethylsilyl)ethoxymethyl prior to reaction.

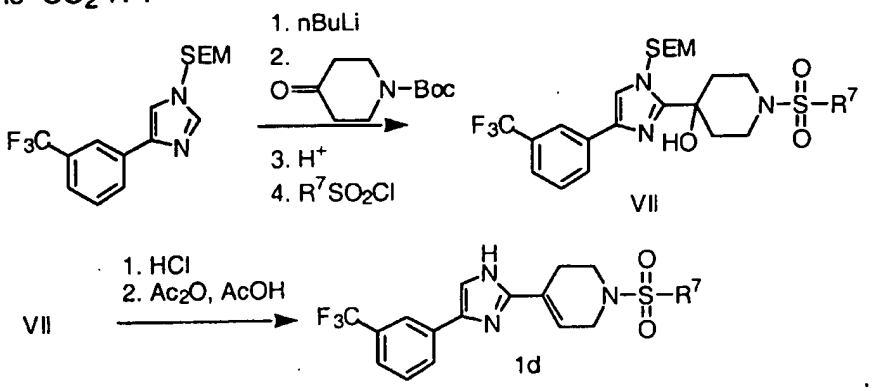
Scheme 2:

Compounds of formula 1c wherein X is =CH- can be prepared by reacting an N-protected (CF_3-phenyl)-substituted imidazole of formula II with an R-containing reagent, for example an R-boronic acid of formula III, followed by deprotection of the resultant intermediate of formula IV, as shown in the following typical reaction scheme, wherein SEM is (2-trimethylsilyl)ethoxymethyl:

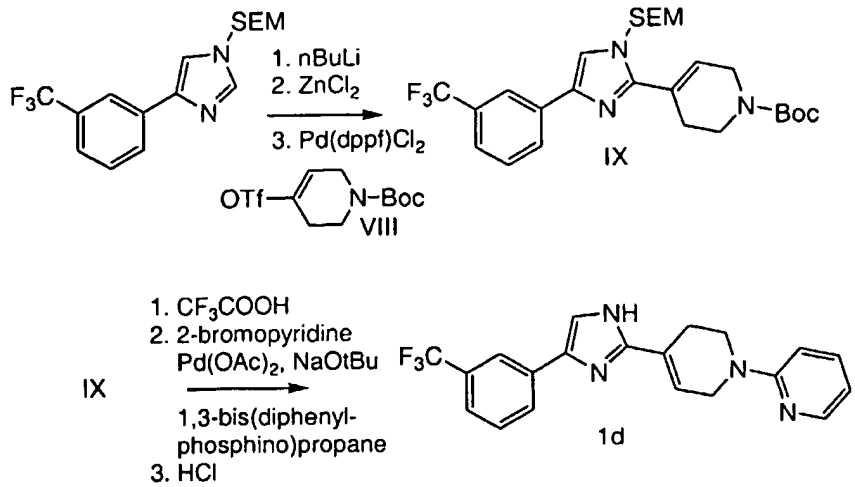


Scheme 3:

Compounds of formula 1d wherein R is a substituted 1,2,5,6-tetrahydropyridyl of the formula  can be prepared by reacting an N-protected (CF_3-phenyl)-substituted imidazole with an N-protected 4-piperidone, followed by dehydration of the resultant intermediate of formula VII, as shown in the following typical reaction scheme wherein R^8 is $-SO_2-R^7$:



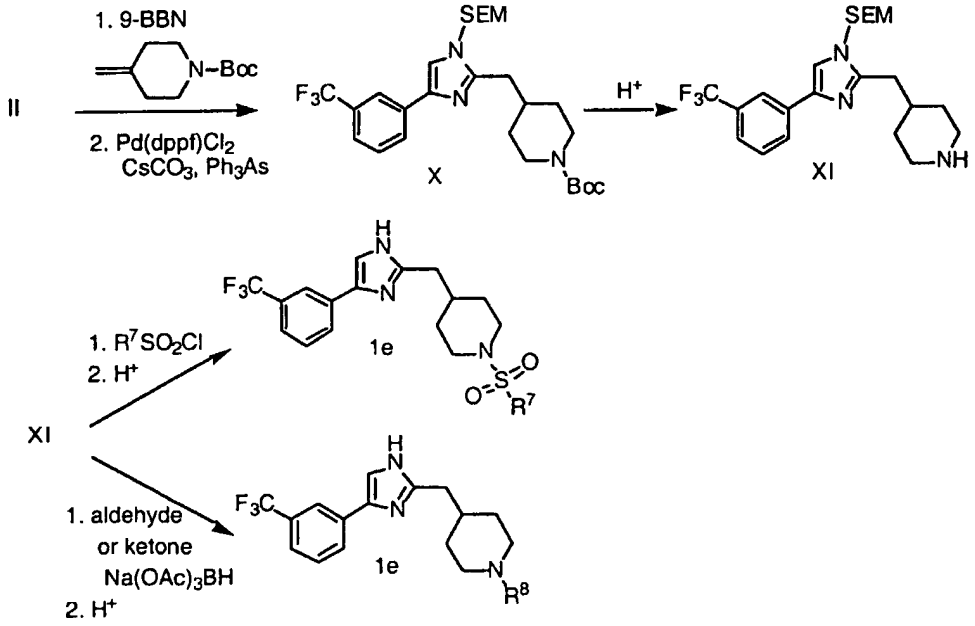
Alternatively, compounds of formula 1d wherein X is =CH- can be prepared by reacting an N-protected (CF_3-phenyl)-substituted imidazole with an N-protected 4-(trifluoromethanesulfonyloxy)-1,2,5,6-tetrahydropyridine of formula VIII, followed by deprotection of the resultant intermediate of formula IX.



Compounds of formula 1d can be converted to compounds of formula I wherein R is N-substituted-4-piperidyl by reducing the compound of formula 1d, for example by hydrogenation.

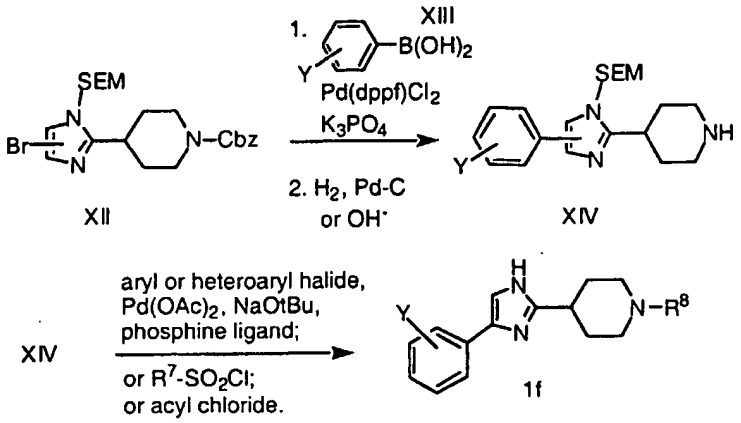
Scheme 4:

Compounds of formula 1e wherein R is an N-R^8-substituted piperidinylmethyl can be prepared by reacting an N-protected (CF_3-phenyl)-substituted imidazole of formula II with an N-protected 4-methylenepiperidine. After deprotection of the piperidinyl moiety of the resultant intermediate of formula X, using procedures well known in the art, the piperidyl nitrogen on the intermediate of formula XI is substituted with R^8 and the protecting group on the imidazolyl nitrogen is removed:

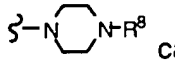


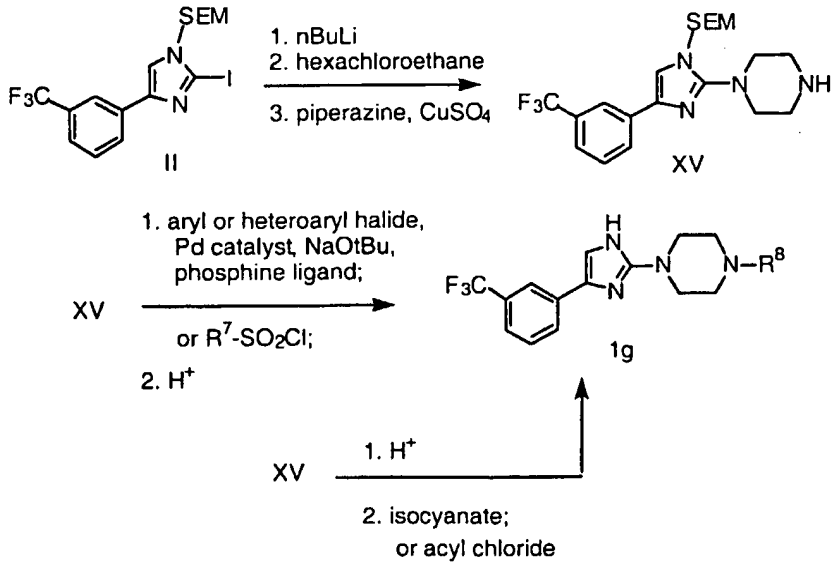
Scheme 5

A method of preparation of compounds of formula 1f wherein R is N-substituted-4-piperidyl is by reacting a 5- (or 4-) -bromo-2-(N-protected-4-piperidyl)imidazole of formula XII with an aryl boronic acid of formula XIII. After deprotection of the piperidinyl moiety of the resultant intermediate, using procedures well known in the art, the piperidyl nitrogen on the intermediate of formula XIV is substituted with R^8 and the protecting group on the imidazole nitrogen is removed.

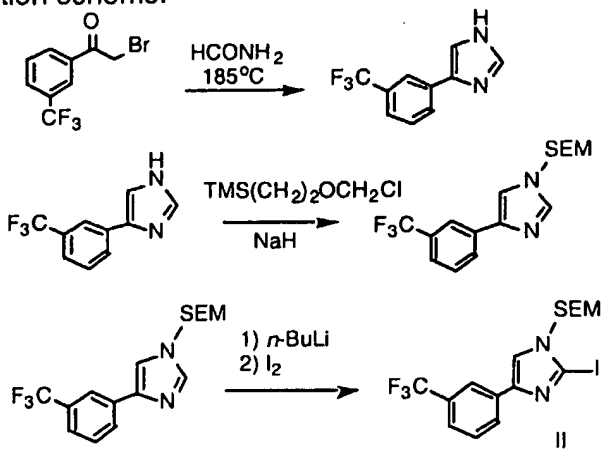


Scheme 6

Compounds of formula 1g wherein R is a substituted piperazinyl of the formula  can be prepared by reacting an N-protected phenyl-substituted imidazole with piperazine. Derivitization of the resultant intermediate of formula XV is followed by deprotection of the imidazole nitrogen by methods known to those skilled in the art to give compounds of fourmula 1g where R_8 is aryl, heteroaryl, or R_7-SO_2-. Alternatively, the imidazole nitrogen of intermediate XV is deprotected, and the piperazine nitrogen of the resultant intermediate is reacted with an isocyanate or an acyl chloride to give compounds of formula 1g where R^8 is $-CONR^4R^5$, $-CO-(C_1-C_6)$-alkyl, $-CO(C_3-C_7)$cycloalkyl, -C(O)aryl, C(O)heteroaryl.

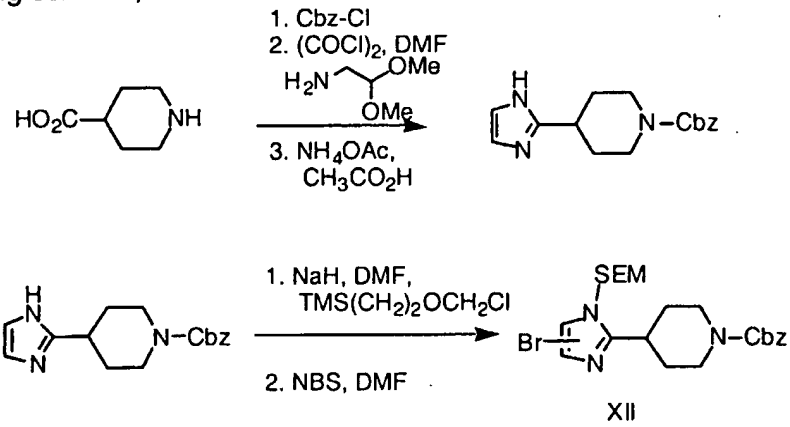


Starting materials of formula II are prepared according to the following reaction scheme:



α-Bromo-(3-trifluoromethyl)acetophenone is condensed with formamide and a (2-trimethylsilyl)ethoxymethyl group is placed on the imidazole nitrogen. The 2-position of the imidazolyl group is iodinated to obtain the starting material of formula II.

Starting material of formula XII is prepared according to the following scheme;



XII

Isonipecotic acid is condensed with aminoacetaldehyde dimethyl acetal and the product is reacted with ammonium acetate to form an imidazole substituted at the 2-position by N-protected 4-piperidinyl. A (2-trimethylsilyl)ethoxyoxymethyl group is placed on the imidazole nitrogen and the resultant product is brominated to give a mixture of regioisomeric 4- and 5-bromoimidazoles of formula XII.

The pyridyl amidine shown in Scheme 1 is prepared by treating 3-cyanopyridine with an ammonia equivalent such as LHMDS or methylchloroaluminum amide.

Substituted amidines used in the method of Scheme 1 are known or can be prepared by known procedures.

The compounds of formula I exhibit selective neuropeptide Y Y5 antagonizing activity, which has been correlated with pharmaceutical activity for treating eating disorders, such as obesity and hyperphagia, and diabetes.

The compounds of formula I display pharmacological activity in test procedures designated to indicate neuropeptide Y Y5 receptor antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses. Following are descriptions of the test procedures.

cAMP Assay

CHO cells expressing NPY Y_5 receptors were maintained in Ham's F-12 media (Gibco-BRL) supplemented with 10% FCS (ICN), 1% penicillin-streptomycin, 1% non-essential amino acids and 200 μg/ml Geneticin (GibcoBRL #11811-031) under a humidified 5% CO_2 atmosphere. Two days prior to assay, cells were released from T-175 tissue culture flasks using cell dissociation solution (1X; non-enzymatic [Sigma #C-5914]) and seeded into 96-well, flat-bottom tissue culture plates at a density of 15,000 to 20,000 cells per well. After approximately 48 hours, the cell monolayers were rinsed with Hank's balanced salt solution (HBSS) then preincubated with approximately 150 μl/well of assay buffer (HBSS supplemented with 4 mM $MgCl_2$, 10 mM HEPES, 0.2% BSA [HH]) containing 1 mM 3-isobutyl-1-methylxanthine ([IBMX] Sigma #I-5879) with or without the antagonist compound of interest at 37°C. After 20 minutes the 1 mM IBMX-HH assay buffer (± antagonist compound) was removed and replaced with assay buffer containing 1.5 μM forskolin (Sigma #F-6886) and various concentrations of NPY in the presence or absence of one concentration of the antagonist compound of interest. At the end of 10 minutes, the media were removed and the cell monolayers treated with 75 μl ethanol. The tissue culture plates were agitated on a platform shaker for 15 minutes, after which the plates were transferred to a warm water bath in order to evaporate the ethanol. Upon

bringing all wells to dryness, the cell residues were resolubilized with 250 μl FlashPlate assay buffer. The amount of cAMP in each well was quantified using the [^{125}I]-cAMP FlashPlate kit (NEN #SMP-001) and according to the protocol provided by the manufacturer. Data were expressed as either pmol cAMP/ml or as percent of control. All data points were determined in triplicate and EC_{50}'s (nM) were calculated using a nonlinear (sigmoidal) regression equation (GraphPad Prism^{TM}). The K_B of the antagonist compound was estimated using the following formula:

$$K_B = [B] / (1 - \{[A'] / [A]\})$$

where [A] is the EC_{50} of the agonist (NPY) in the absence of antagonist, [A'] is the EC_{50} of the agonist (NPY) in the presence of antagonist, and [B] is the concentration of the antagonist.

NPY Receptor Binding Assay

Human NPY Y_5 receptors were expressed in CHO cells. Binding assays were performed in 50 mM HEPES, pH 7.2, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA containing 5-10 μg of membrane protein and 0.1 nM ^{125}I-peptide YY in a total volume of 200 μl. Non-specific binding was determined in the presence of 1 uM NPY. The reaction mixtures were incubated for 90 minutes at room temperature, then filtered through Millipore MAFC glass fiber filter plates which had been pre-soaked in 0.5% polyethyleneimine. The filters were washed with phosphate-buffered saline, and radioactivity was measured in a Packard TopCount scintillation counter.

For the compounds of this invention, a range of neuropeptide Y5 receptor binding activity from about 0.5 nM to about 1000 nM was observed. Compounds of this invention preferably have a binding activity in the range of about 0.5 nM to 500 nM, more preferably about 0.5 to 100 nM, and most preferably about 0.5 to 10 nM.

Neuropeptide Y Y5 receptor binding activity results for representative compounds of the invention are as follows:

Ex.	r/h Y5 Ki nM
1A	3
1B	52
2A	315
3	17
5A	1.4
6A	2.1
10A	63
19	1.7
21C	2
26	1.4

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

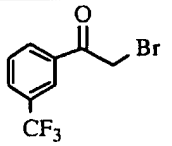
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

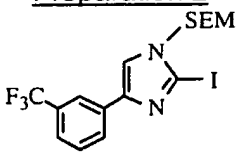
In the preparations and examples, the following abbreviations are used: room temperature (R.T.), phenyl (Ph), acetyl (Ac), ether (Et_2O), ethyl acetate (EtOAc), dimethylformamide (DMF), tetrabutyl ammonium fluoride (TBAF), tetrahydrofuran (THF), ethanol (EtOH), lithium aluminum hydride (LAH), 4-(dimethylamino)pyridine (DMAP), preparative thin layer chromatography (PTLC), 1,1'-bis(diphenylphosphino)ferrocene (dppf), lithium hexamethyldisilazide (LHMDS) and 1-(3-dimethyl(aminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI).

Preparation 1

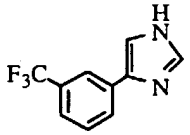


To a stirred solution of 3'-(trifluoromethyl)acetophenone (4.0 ml, 26 mmol) in Et_2O (26 ml) under N_2 was added bromine (1.4 ml, 26 mmol) dropwise over 1 h. The reaction was stirred at R.T. for 30 min., then poured slowly into sat'd $NaHCO_3$. The organic portion was washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (2:3 CH_2Cl_2/hexanes) yielded Preparation 1 (4.3 g, 61 %). ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.24 (d, 1H, J=7.8 Hz), 7.93 (d, 1H, J=7.8 Hz), 7.72 (t, 1H, J=7.8 Hz), 4.52 (s, 2H).

Preparation 2



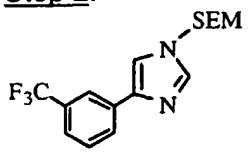
Step 1:



A solution of Preparation 1 (5.53 g, 20.7 mmol) in formamide (32 ml) was heated at 185°C in a sealed pressure tube for 3 h. The reaction mixture was allowed to cool to R.T., then poured into aqueous sat'd $NaHCO_3$ solution (120 ml) and extracted with EtOAc (2x100 ml). The organic layer was washed with water (60 ml) and sat'd NaCl (60 ml), then dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography (CH_2Cl_2, then gradient of increasing CH_3OH

concentration to 5:95 CH_3OH/CH_2Cl_2) gave a white solid (3.83 g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (bs, 1H), 8.01 (m, 1H), 7.90 (bs, 1H), 7.57 (m, 2H), 7.49 (bs, 1H). MS *m/e* 213 $(M+H)^+$.

Step 2:



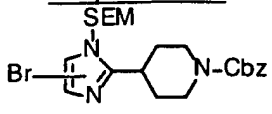
To a stirred, ice-cold solution of the product of Step 1 (0.70 g, 3.3 mmol) in THF (13 ml) under N_2 was added 95% NaH (0.10 g, 4.3 mmol). After 20 min., (2-trimethylsilyl)ethoxymethyl chloride (0.70 ml, 4.0 mmol) was added dropwise over 5 min. The reaction was warmed to R.T. After 2 h, Et_2O was added, and the whole washed with water, dried ($MgSO_4$), filtered and concentrated under vacuum. Purification by flash chromatography (20:80, then 40:60 EtOAc/hexanes) yielded the product (0.69 g, 61%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (bs, 1H), 8.03 (m, 1H), 7.74 (d, 1H, *J*=1.3 Hz), 7.56 (m, 2H), 7.47 (d, 1H, *J*=1.3 Hz), 5.38 (s, 2H), 3.60 (t, 2H, *J*=8.2 Hz), 1.00 (t, 2H, *J*=8.2 Hz), 0.07 (s, 9H). HRMS: Calcd for $C_{16}H_{21}N_2OF_3Si$ $(M+H)^+$: 343.1454. Found: 343.1452.

Step 3:

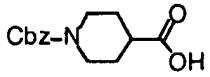
A 1.6N solution of *n*-BuLi in hexanes (1.4 ml, 2.3 mmol) was added dropwise to a stirred -78°C solution of the product of Step 2 (0.52 g, 1.5 mmol) in THF (15 ml) under N_2. Immediately after the addition was complete, a solution of iodine (0.58 g, 2.3 mmol) in THF (4.5 ml) was added dropwise over 10 min. After warming to R.T. over 1 h, the reaction was diluted with CH_2Cl_2 and water. The organic layer was washed with sat'd aqueous $Na_2S_2O_3$ and water, then dried ($MgSO_4$), filtered and concentrated under vacuum to give the title compound (0.71 g) which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (bs, 1H), 7.99 (m, 1H), 7.56 (m, 3H), 5.34 (s, 2H), 3.65 (t, 2H, *J*=8.2 Hz), 1.02 (t, 2H, *J*=8.2 Hz), 0.07 (s, 9H).

MS *m/e* 469 $(M+H)^+$.

Preparation 3

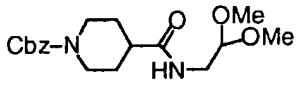


Step 1:



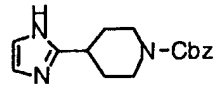
Isonipecotic acid (5.118 g, 39.63 mmol) and potassium carbonate (12.94 g, 93.63 mmol) were dissolved in water (52 ml). The solution was cooled in an ice-water bath and benzyl chloroformate (7.3 ml, 51 mmol) was added dropwise. The mixture was brought to R.T. and stirred for 16 h. The reaction was extracted with EtOAc (3x30 ml). The aqueous layer was acidified to pH 1~2 with conc. HCl (15 ml) and then extracted with CH_2Cl_2 (3x60 ml). The combined organic layer was dried (Na_2SO_4) and concentrated to give the product (10.306 g, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (5H, m), 5.11 (2H, s), 4.09 (2H, m), 2.93 (2H, m), 2.50 (1H, m), 1.90 (2H, m), 1.67 (2H, m).

Step 2:



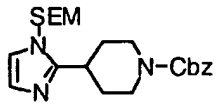
To a solution of the product of Step 1 (10.306 g, 39.186 mmol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (5.138 g, 39.67 mmol) and drops of DMF. The solution was stirred at R.T. for 16 h. More CH_2Cl_2 (50 ml) was added and the solution was cooled in an ice-water bath. Triethylamine (11.99 g, 118.5 mmol) and aminoacetaldehyde dimethylacetal (4.183 g, 39.79 mmol) were added and the reaction was stirred at R.T. for 16 h. The mixture was washed with water (200 ml), saturated NH_4Cl (150 ml), 1N NaOH (200 ml), and brine (200 ml). The organic layer was dried (K_2CO_3), concentrated, and purified by a flash column (CH_2Cl_2, then gradient of increasing concentration of MeOH to 1.5:98.5 MeOH/CH_2Cl_2) to give the product (10.096 g, 74%). MS (ES) *m/e* 351 $(M+H)^+$.

Step 3:



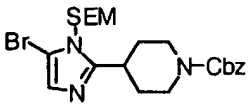
A solution of the product of Step 2 (5.09 g, 14.5 mmol) and ammonium acetate (32.0 g, 415 mmol) in glacial acetic acid (25 ml) was refluxed for 5 h. The volatiles were evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 (2x100 ml) and aqueous NH_4OH (80 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by a flash column (hexanes, then gradient of increasing EtOAc concentration to 100% EtOAc) to give the product (1.909 g, 46%).
MS (ES) *m/e* 286 $(M+H)^+$.

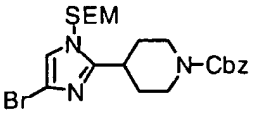
Step 4:



A mixture of the product of Step 3 (1.844 g, 6.471 mmol) and 60% sodium hydride dispersion in mineral oil (0.355 g, 8.875 mmol) in dry DMF (20 ml) was stirred for 1 h. (2-Trimethylsilyl)ethoxymethyl chloride (1.396 g, 7.643 mmol) was added and the mixture was stirred for 3 days. DMF was evaporated *in vacuo* and the residue was partitioned between EtOAc (100 ml) and water (3x100 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by a flash column (1:99 MeOH/CH_2Cl_2, then 2:98 MeOH/CH_2Cl_2) yielded the product (2.420 g, 90%).
MS (ES) *m/e* 416 $(M+H)^+$.

Step 5:

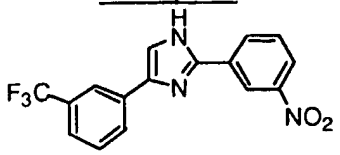




To an ice-cold solution of the product of Step 4 (1.601 g, 3.858 mmol) in DMF (15 ml) was added N-bromosuccinimide (0.383 g, 2.15 mmol). After 0.5 h another portion of N-bromosuccinimide (0.313 g, 1.76 mmol) was added. The solution was warmed to R.T. and stirred for 3 h. DMF was evaporated *in vacuo* and the residue was partitioned between EtOAc (200 ml) and 0.5N NaOH (80 ml). The organic layer was washed with water (100 ml) and dried over $MgSO_4$. Evaporation followed by flash chromatography (CH_2Cl_2, then gradient of increasing MeOH concentration to 1:99 MeOH/CH_2Cl_2) gave the product as a mixture of 4- and 5-bromo regioisomers. Major, more polar isomer (1.042 g, 54%), MS (ES) *m/e*

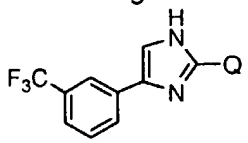
496 $(M+H)^+$. Minor regioisomer (0.339 g, 18%), MS (ES) *m/e* 496 $(M+H)^+$.

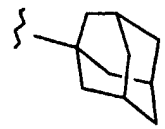
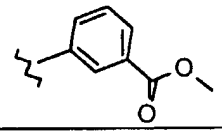
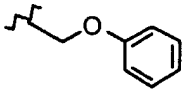
Example 1

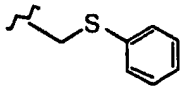
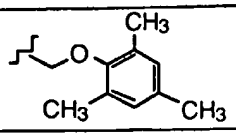


To a stirred solution of 3-nitrobenzamidine (5.4 g, 33 mmol) in DMF (80 ml) was added Na_2CO_3 (2.8 g, 26 mmol) followed by Preparation 1 (3.4 g, 13 mmol), and the mixture was heated at 80 °C for 5 h. The reaction mixture was diluted with EtOAc and washed several times with H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residue (1:99 CH_3OH/ CH_2Cl_2) afforded the product (3.73 g, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (1H, bs), 8.41 (1H, d, *J*=7.7 Hz), 8.28 (1H, d, *J*=8.2 Hz), 8.14 (s, 1H), 8.07 (m, 1H), 7.70 (1H, t, *J*=7.9 Hz), 7.59 (m, 3H). HRMS (FAB): Calcd. for $C_{16}H_{10}N_3O_2F_3$ $(M+H)^+$: 334.0803. Found: 334.0815.

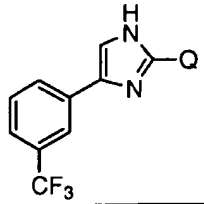
Using appropriate starting materials and essentially the same procedure, compounds of the following structure were prepared:

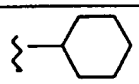
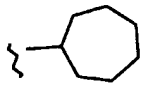
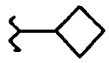
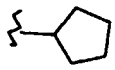
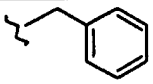


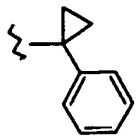
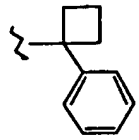
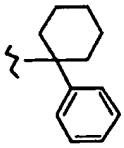
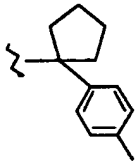
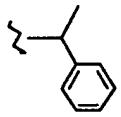
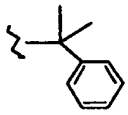
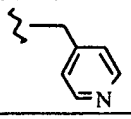
Ex.	Q	MF	HRMS Calculated	HRMS Found
1A		$C_{20}H_{21}N_2F_3$	347.1735	347.1738
1B		$C_{18}H_{13}N_2O_2F_3$	347.1007	347.1012
1C	$-CH_3$	$C_{11}H_9N_2F_3$	227.0796	227.0797
1D		$C_{17}H_{13}N_2OF_3$	319.1058	319.1055
1E	$-C(CH_3)_3$	$C_{14}H_{15}N_2F_3$	269.1266	269.1261
1F	$-CF_3$	$C_{11}H_6N_2F_6$	281.0513	281.0510

1G		$C_{17}H_{13}N_2SF_3$	335.0830	335.0829
1H		$C_{20}H_{19}N_2OF_3$	361.1528	361.1531

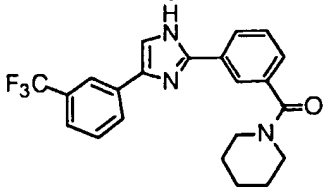
The following compounds were prepared by condensation of the appropriate amidine and the product of Preparation 1 by essentially the same procedure, except that the requisite amidines were prepared from $CH_3Al(Cl)NH_2$ (the preparation of which is described in Example 7, Step 1) and the appropriate nitrile by the procedure described in Example 7, Step 2.



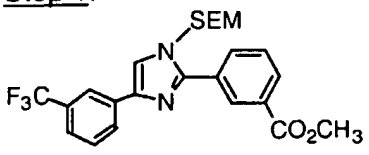
Ex.	Q	Physical Data
1I		HRMS: calc. 295.1422 found 295.1431
1J		MS: 309 $(M+H)^+$
1K		HRMS: calc. 253.0953 found 253.0944
1L		HRMS: calc. 267.1109 found 267.1100
1M		HRMS: calc. 281.1266 found 281.1266
1N		HRMS: calc. 303.1109 found 303.1110

1O		MS: 329 $(M+H)^+$
1P		MS: 343 $(M+H)^+$
1Q		MS: 371 $(M+H)^+$
1R		MS: 371 $(M+H)^+$
1S		MS: 317 $(M+H)^+$
1T		MS: 331 $(M+H)^+$
1U		MS: 304 $(M+H)^+$

Example 2



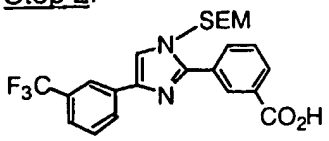
Step 1:



5

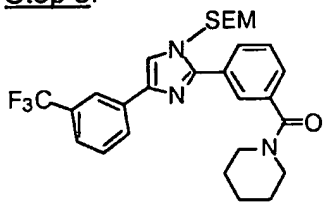
Using the procedure of Preparation 2, Step 2, reaction of the product of Example 1B (0.98 g, 2.8 mmol) with NaH and (2-trimethylsilyl)-ethoxymethyl chloride afforded the product (1.1 g, 85%).

Step 2:



The product of Step 1 (1.1 g, 2.3 mmol) was dissolved in CH_3OH (30 ml) and H_2O (10 ml), then $LiOH \cdot H_2O$ (0.49 g, 12 mmol) was added. The reaction mixture was stirred for 15 h at R.T., acidified with 1 N HCl and extracted with CH_2Cl_2. The organic layer was evaporated to give the product (0.98 g, 92%), which was used in Step 3 without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (m, 1H), 8.16 (m, 4H), 7.65 (t, 1H, *J*=7.6 Hz), 7.57 (m, 3H), 5.41 (s, 2H), 3.70 (t, 2H, *J*=8.3 Hz), 1.04 (t, 2H, *J*=8.3 Hz), 0.06 (s, 9H). MS (CI) m/e 463 $(M+H)^+$.

Step 3:



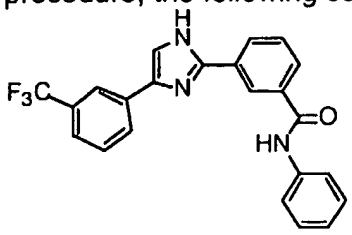
To a solution of the product of Step 2 (50 mg, 0.11 mmol), EDCI (31 mg, 0.16 mmol) and DMAP (14 mg, 0.11 mmol) in CH_2Cl_2 (1.0 ml) was added piperidine (10 μL, 0.13 mmol). The reaction was stirred at R.T. for 17 h, then more EDCI (17 mg, 0.090 mmol) and DMAP (7.0 mg, 0.055 mmol) were added. The reaction was stirred for an additional 48 h, washed with 1 N NaOH, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated under vacuum. Purification via PTLC (5:95 CH_3OH/ CH_2Cl_2) yielded the product as a solid (41 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (m, 1H), 8.07 (m, 1H), 7.95 (dd, 1H, *J*=1.6, 7.5 Hz), 7.90 (m, 1H), 7.62-7.51 (m, 5H), 5.35 (s, 2H), 3.78 (br s, 2H), 3.68 (t, 2H, *J*=8.2 Hz), 3.43 (br s, 2H), 1.59-1.74 (m, 6H), 1.01 (t, 2H, *J*=8.2 Hz), 0.06 (s, 9H). HRMS (FAB): Calc'd for $C_{28}H_{34}N_3O_2F_3Si$ $(M+H)^+$ 530.2451. Found: 530.2440.

Step 4:

A solution of the product of Step 3 (41 mg, 0.080 mmol) in CH_3OH

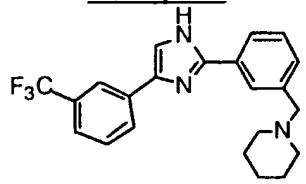
(3.0 ml) and 6 N HCl (3.0 ml) was refluxed for 3 h. After cooling to R.T., the reaction was diluted with CH_2Cl_2, washed with 1 N NaOH, dried over K_2CO_3, filtered and concentrated under vacuum to give the crude product (25 mg, 79%), which was purified by PTLC (1:99 CH_3OH/ CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 8.01 (m, 2H), 7.85 (m, 1H), 7.54 (m, 2H), 7.49 (s, 1H), 7.36 (t, 1H, *J*=7.7 Hz), 7.22 (m, 1H), 3.82 (m, 2H), 3.41 (m, 2H), 1.76 (bs, 4H), 1.59 (m, 2H). MS (CI) m/e 400 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure, the following compound was also prepared:



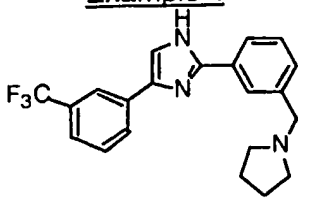
2A MS 408 $(M+H)^+$

Example 3

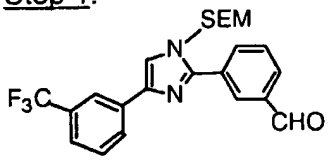


To a solution of Example 2 (20 mg, 0.050 mmol) in THF (1.8 ml) was added LAH (3.0 mg, 0.08 mmol). The reaction was stirred for 15 h at R.T., then more LAH (6.0 mg, 0.16 mmol) was added. The reaction was stirred for an additional 5 h, then 1 N NaOH was added. The mixture was extracted with CH_2Cl_2, dried over K_2CO_3, filtered and concentrated under vacuum. Purification by PTLC (5:95 CH_3OH/ CH_2Cl_2) yielded the title compound (10 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96-8.17 (m, 2H), 7.81-7.96 (m, 2H), 7.51 (m, 2H), 7.30-7.47 (m, 3H), 3.54 (s, 2H), 2.46 (bs, 4H), 1.63 (quintet, 4H, *J*=5.2 Hz), 1.49 (m, 2H). HRMS (FAB): Calc'd for $C_{22}H_{20}N_3F_3$ $(M+H)^+$: 386.1844. Found: 386.1836.

Example 4

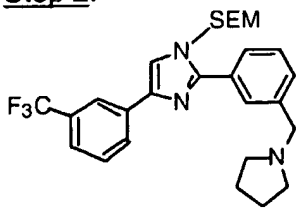


Step 1:



A mixture of Preparation 2 (661 mg, 1.41 mmol), 3-formyl-benzeneboronic acid (433 mg, 2.88 mmol), $Pd(dppf)Cl_2$ (120 mg, 0.147 mmol), and K_3PO_4 (660 mg, 3.08 mmol) in 1,2-dimethoxyethane (11 ml) was purged with N_2, and heated at 95 °C overnight in a sealed vessel. The reaction mixture was allowed to cool, diluted with CH_2Cl_2 (60 ml), and filtered. The filtrate was washed with water (30 ml), dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by flash chromatography (CH_2Cl_2, then 1:99 CH_3OH/CH_2Cl_2) afforded the product (492 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.39 (s, 1H), 8.2-7.9 (m, 4H), 7.67 (m, 1H), 7.52 (m, 3H), 5.33 (s, 2H), 3.66 (m, 2H), 0.98 (m, 2H), -0.02 (s, 9H).

Step 2:



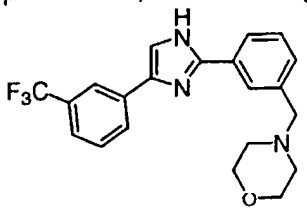
A mixture of the product of Step 1 (30 mg, 0.067 mmol), pyrrolidine (15 µl, 0.18 mmol), and sodium triacetoxyborohydride (22 mg, 0.10 mmol) in 1,2-dichloroethane (2 ml) was strirred overnight. The mixture was partitioned between CH_2Cl_2 (35 ml) and 1N NaOH (10 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the residue by PTLC (5:95 CH_3OH/CH_2Cl_2) gave the product (31 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.02 (m, 1H), 7.73 (m, 1H),

7.67 (m, 1H), 7.53-7.37 (m, 5H), 5.31 (s, 2H), 3.67 (s, 2H), 3.56 (m, 2H), 2.54 (bm, 4H), 1.78 (bm, 4H), 0.92 (m, 2H), -0.04 (s, 9H).

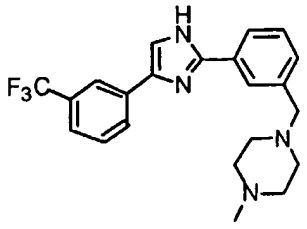
Step 3:

Reaction of the product of Step 2 (31 mg, 0.063 mmol) with aqueous HCl/CH_3OH using the procedure of Example 2, Step 4, afforded the product (19 mg, 81%). ^1H NMR (400 MHz, CD_3OD): δ 8.13 (s, 1H), 8.03 (m, 1H), 7.92 (s, 1H), 7.86 (m, 1H), 7.65 (s, 1H), 7.60-7.40 (m, 4H), 3.72 (s, 2H), 2.60 (m, 4H), 1.82 (m, 4H). MS (CI) m/e 372 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure, the following compounds were prepared:

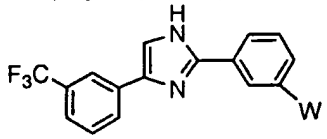


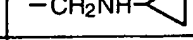
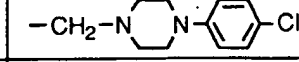
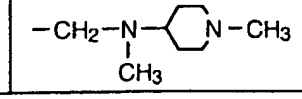
4A MS (FAB) m/e 388 $(M+H)^+$

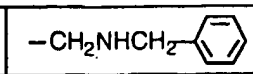
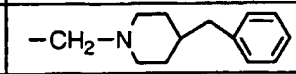
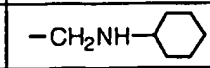
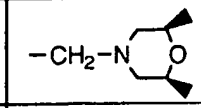
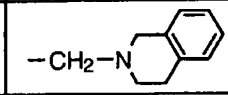
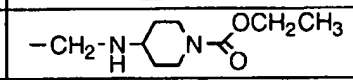
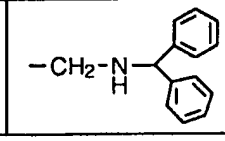


4B MS (FAB) m/e 401 $(M+H)^+$

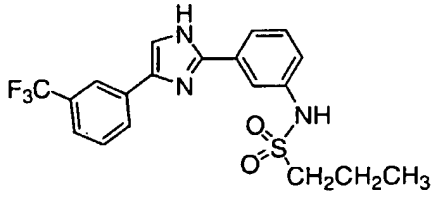
Using appropriate amines, the following compounds were prepared from the product of Example 4, Step 1 by the procedure of Example 4, except that the order of the reductive amination and the cleavage of the (2-trimethylsilyl)-ethoxymethyl group (Steps 2 and 3) was reversed:



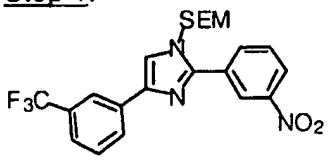
Ex.	W	Data
4C		MS (CI) 358 $(M+H)^+$
4D	$-CH_2NHCH_2CH_2OH$	MS (FAB) 362 $(M+H)^+$
4E	$-CH_2NH(CH_2)_2N(CH_3)_2$	MS (CI) 389 $(M+H)^+$
4F		MS (FAB) 497 $(M+H)^+$
4G		MS (CI) 429 $(M+H)^+$

4H		MS (CI) 408 (M+H)$^+$
4I		MS (CI) 476 (M+H)$^+$
4J		MS (FAB) 400 (M+H)$^+$
4K		MS (CI) 416 (M+H)$^+$
4L		MS (CI) 434 (M+H)$^+$
4M		MS (CI) 473 (M+H)$^+$
4N		MS (CI) 484 (M+H)$^+$

Example 5



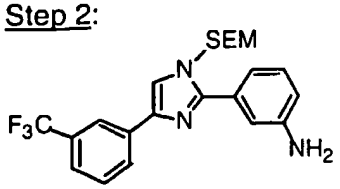
Step 1:



To a stirred, ice-cold solution of the product of Example 1 (3.70 g, 11.1 mmol) in THF (95 ml) was added NaH (0.32 g, 13 mmol). After 10 min., (2-trimethylsilyl)ethoxymethyl chloride (2.2 ml, 12 mmol) was added, and the reaction mixture was stirred at RT for 6 h. The reaction mixture was diluted with Et_2O, washed with H_2O and sat'd NaCl, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (4:1 hexanes/EtOAc) afforded the product (4.08 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (1H, t, J=2.0 Hz), 8.35 (1H, m), 8.33 (1H, m), 8.14 (1H, m), 8.08 (1H, m), 7.72 (1H, t, J=8.0 Hz), 7.56 (3H, m), 5.38 (2H, s), 3.76 (2H, t, J=8.6 Hz),

1.08 (2H, t, *J*=8.6 Hz), 0.06 (9H, s). HRMS (FAB): Calcd. for $C_{22}H_{24}N_3O_3F_3Si$ $(M+H)^+$: 464.1617. Found: 464.1629.

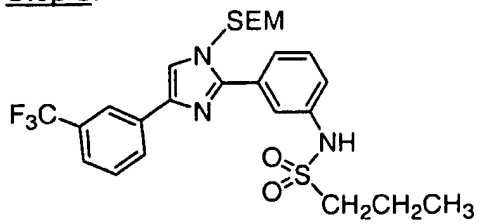
Step 2:



To a solution of the product of Step 1 (3.91 g, 8.40 mmol) in EtOH (100 ml) was added 10% Pd/C (0.4 g) and the mixture was purged with H_2. After 8 h under H_2 balloon pressure, the mixture was filtered through celite and the filter pad was washed with EtOH. The combined filtrate and washings were concentrated under vacuum to give the product (3.47 g, 95%) which was used in Step 3 without further purification. An analytical sample was isolated by PTLC (1:99 CH_3OH/CH_2Cl_2).

^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s), 8.07 (1H, m), 7.53 (2H, m), 7.50 (1H, s), 7.29 (1H, m), 7.18 (2H, m), 6.81 (1H, m), 5.35 (2H, s), 3.63 (2H, t, *J*=8.2 Hz), 0.97 (2H, t, *J*=8.2 Hz), 0.04 (9H, s). MS (CI) 434 $(M+H)^+$.

Step 3:



To solution of the product of Step 2 (123 mg, 0.29 mmol) in CH_2Cl_2 (5 ml) under N_2 was added pyridine (400 μl) and *n*-propylsulfonyl chloride (160 μl, 1.4 mmol). The reaction mixture was stirred at R.T.for 16 h, then partitioned between water and CH_2Cl_2. The organic layer was dried (K_2CO_3), filtered and concentrated. The residue was subjected to PTLC (2:98 CH_3OH/CH_2Cl_2) to afford the product (114 mg, 73%).

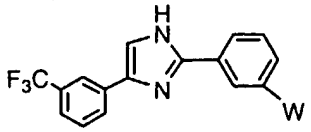
^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s), 8.06 (1H, m), 7.78 (2H, m), 7.48–7.59 (3H, m), 7.41 (1H, m), 6.79 (1H, bs), 5.38 (2H, s), 3.69 (2H, t, *J*=8.2 Hz), 3.16 (2H, m), 1.92 (2H, m), 1.08 (3H, t, *J*=7.4 Hz), 1.02 (2H, t, *J*=8.2 Hz), 0.06 (9H, s). HRMS (FAB): Calcd. for $C_{25}H_{32}N_3O_3SF_3Si$ $(M+H)^+$: 540.1963 Found: 540.1937.

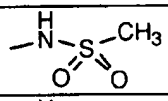
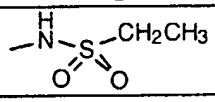
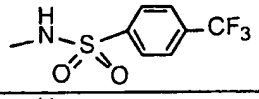
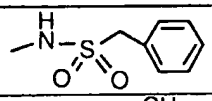
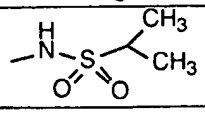
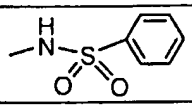
Step 4:

A mixture of the product of Step 3 (114 mg, 0.21 mmol), 5 N HCl (5 ml), and CH_3OH (5 ml) was refluxed for 3 h. The reaction mixture was allowed to cool, sat'd $NaHCO_3$ was cautiously added, and the whole was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to PTLC to afford the product (84 mg, 95%).

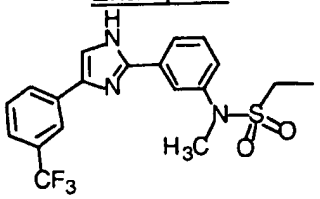
^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.96 (1H, d, *J*=7.3 Hz), 7.80 (1H, d, *J*=7.7 Hz), 7.76 (1H, m), 7.65–7.46 (3H, m), 7.38 (1H, t, *J*=7.9 Hz), 7.28 (1H, m), 3.15 (2H, m), 1.89 (2H, m), 1.03 (3H, t, *J*=7.4 Hz). HRMS (FAB): Calcd. for $C_{19}H_{18}N_3O_2SF_3$ $(M+H)^+$: 410.1150 Found: 410.1160.

Using appropriate starting materials and essentially the same procedure, the following compounds were prepared:

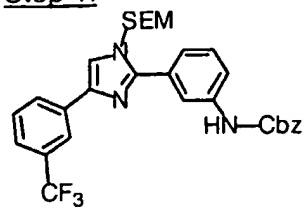


Ex.	W	Data
5A		MS (FAB) 382 $(M+H)^+$
5B		MS (FAB) 396 $(M+H)^+$
5C		MS (CI) 512 $(M+H)^+$
5D		MS (FAB) 458 $(M+H)^+$
5E		MS (FAB) 410 $(M+H)^+$
5F		MS (FAB) 444 $(M+H)^+$

Example 6

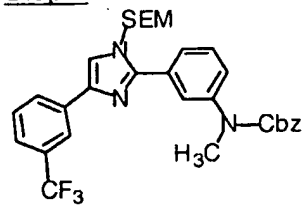


Step 1:



To a solution of the product of Example 5, Step 2 (581 mg, 1.34 mmol) and diisopropylamine (0.30 ml, 1.7 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added benzyl chloroformate (0.22 ml, 1.5 mmol). The mixture was allowed to warm to R.T. and stirred for 60 h. The solution was diluted with CH_2Cl_2 (75 ml) and washed with 1N HCl (25 ml) and 1N NaOH (25 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatograpy (CH_2Cl_2, then gradient of increasing concentration to 6:1000 CH_3OH/CH_2Cl_2 gave the product (732 mg, 96%). MS (ES) m/e 568 $(M+H)^+$.

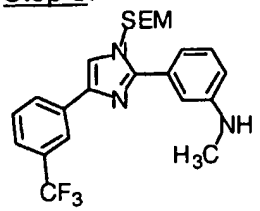
Step 2:



A mixture of the product of Step 1 (732 mg, 1.29 mmol) and 60% NaH in mineral oil (94 mg, 2.4 mmol) in anhydrous DMF (6 ml) was stirred for 1 h. CH_3I (0.15 ml, 2.4 mmol) was added and the stirring continued overnight. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with water (2 x 40 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (hexanes, then gradient of increasing concentration to 1:5 EtOAc/ hexanes) afforded the product (723 mg, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.00 (m, 1H), 7.74 (s, 1H), 7.68 (d, 1H, J=8 Hz),

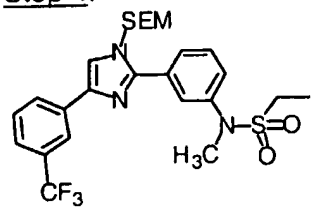
7.27-7.50 (m, 10H), 5.23 (s, 2H), 5.16 (s, 2H), 3.59 (t, 2H, *J*=8 Hz), 3.36 (s, 3H), 0.92 (t, 2H, *J*=8 Hz), -0.02 (s, 9H).

Step 3:



A mixture of the product of Step 2 (732 mg, 1.25 mmol) and 10% Pd/C (112 mg) in 200 proof EtOH (25 ml) was stirred under H_2 (1 atm) for 24 h. The mixture was filtered and the filtrate evaporated to dryness. Purification of the residue by column chromatography (hexanes, then gradient of increasing concentration to 1:9 EtOAc/ hexanes) afforded the product (434 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.01 (m, 1H), 7.47 (m, 3H), 7.27 (m, 1H), 7.04 (m, 2H), 6.67 (m, 1H), 5.31 (s, 2H), 3.85 (b, 1H), 3.56 (t, 2H, *J*=8 Hz), 2.87 (s, 3H), 0.91 (t, 2H, *J*=8 Hz), -0.02 (s, 9H).

Step 4:



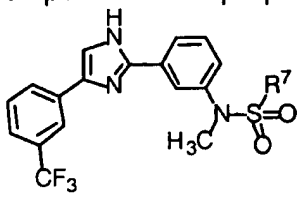
A solution of the product of Step 3 (49 mg, 0.11 mmol), $CH_3CH_2SO_2Cl$ (78 mg, 0.61 mmol) and pyridine (0.24 ml, 3.0 mmol) in anhydrous CH_2Cl_2 (6 ml) was stirred for 7 days. The mixture was diluted with CH_2Cl_2 (45 ml) and washed with 1N NaOH (15 ml), water (20 ml) and saturated NH_4Cl (20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification of the residue by PTLC (1:99 CH_3OH/ CH_2Cl_2) gave the product (51 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.02 (m, 1H), 7.88 (s, 1H), 7.80 (m, 1H), 7.50 (m, 5H), 5.32 (s, 2H), 3.66 (t, 2H, *J*=8 Hz), 3.41(s, 3H), 3.09 (q, 2H, *J*=7.4 Hz), 1.39 (t, 3H, *J*=7.4 Hz), 0.97 (t, 2H, *J*=8 Hz), -0.01 (s, 9H).

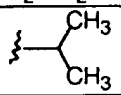
Step 5:

A solution of the product of Step 4 (51 mg, 0.095 mmol) in CH_3OH (7 ml) and 5N HCl (5 ml) was heated to 90 °C for 4 h. After the mixture

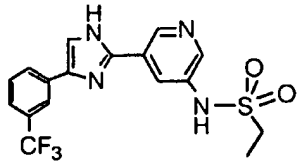
was cooled, it was partitioned between CH_2Cl_2 (50 ml) and aqueous NH_4OH (20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification of the residue by PTLC (1:66 CH_3OH/ CH_2Cl_2) gave the product (38 mg, 98%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.91 (m, 2H), 7.72 (m, 1H), 7.32-7.47 (m, 5H), 3.33 (s, 3H), 3.05 (q, 2H, *J*=7.4 Hz), 1.35 (t, 3H, *J*=7.4 Hz). MS (ES) m/e 410 $(M+H)^+$.

By using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



Ex.	R^7	$(M+H)^+$
6A	$-CH_3$	396
6B	$-CH_2CH_2CH_3$	424
6C		424

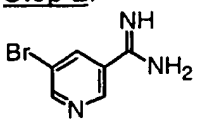
Example 7



Step 1:

To a suspension of NH_4Cl (1.35 g, 25.2 mmol) in anhydrous toluene (15 ml) at 0 °C was added 2.0 M trimethylaluminum in toluene (12.6 ml, 25.2 mmol). After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. This reagent, $CH_3Al(Cl)NH_2$, was used directly in Step 2.

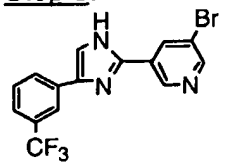
Step 2:



A mixture of the product of Step 1 (22.6 ml, 20.6 mmol) and 5-bromopyridine-3-carbonitrile (1.915 g, 10.46 mmol) in a sealed tube was heated to 95 °C overnight. The mixture was cooled and poured into a

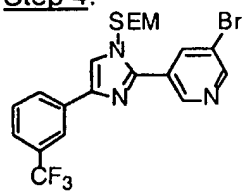
slurry of silica gel (40 g) in $CHCl_3$ (100 ml). This slurry was stirred for 1 h and the silica was filtered off. The filter cake was washed with CH_3OH (200 ml). Evaporation of the filtrate gave the product (2.65 g, 65%). ^1H NMR (CD_3OD, 400 MHz): δ 9.00 (d, 1H, *J*=2.4 Hz), 8.91 (d, 1H, *J*=2 Hz), 8.45 (t, 1H, *J*=2.4 Hz). MS (CI) m/e 200 $(M+H)^+$.

Step 3:



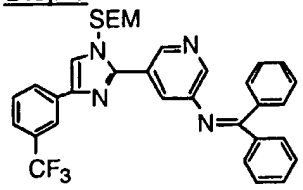
A mixture of the product of Step 2 (1.303 g, 6.6 mmol), Preparation 1 (1.199 g, 4.51 mmol), and Na_2CO_3 (1.15 g, 10.9 mmol) in acetone (20 ml) and DMF (20 ml) was refluxed for 5 h. The solvents were removed under vacuum and the residue was partitioned between water (50 ml) and CH_2Cl_2 (100 ml). The organic layer was washed with water (50 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product was purified by column chromatography (gradient 0.5:99.5 CH_3OH/CH_2Cl_2 to 1.5:98.5 CH_3OH/CH_2Cl_2) to give a light-yellow solid (0.705 g, 42%). ^1H NMR (CD_3OD, 400 MHz): δ 9.10 (d, 1H, *J*=1.6 Hz), 8.66 (d, 1H, *J*=2 Hz), 8.57 (t, 1H, *J*=2 Hz), 8.14 (s, 1H), 8.06 (d, 1H, *J*=6.8 Hz), 7.75 (s, 1H), 7.57 (m, 2H). MS (CI) m/e 368 $(M+H)^+$.

Step 4:



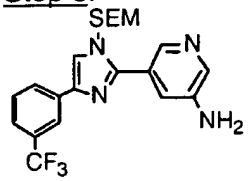
Using the procedure of Example 5, Step 1, reaction of the product of Step 3 (311 mg, 0.845 mmol) with NaH (60% disp., 43 mg, 1.1 mmol) and (2-trimethylsilyl)ethoxymethyl chloride (0.21 ml, 1.07 mmol) afforded the product (292 mg, 69%). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.05 (d, 1H, *J*=2 Hz), 8.74 (d, 1H, *J*=2 Hz), 8.42 (t, 1H, *J*=2 Hz), 8.08 (s, 1H), 8.01 (m, 1H), 7.51 (m, 3H), 5.31 (s, 2H), 3.68 (t, 2H, *J*=8 Hz), 0.99 (t, 2H, *J*=8 Hz), 0.02 (s, 9H).

Step 5:



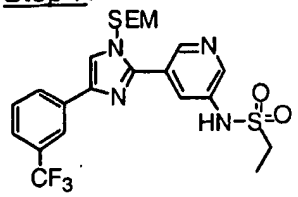
A mixture of the product of Step 4 (114 mg, 0.229 mmol), benzophenone imine (52 mg, 0.29 mmol), sodium *t*-butoxide (35 mg, 0.36 mmol), (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (13 mg, 0.02 mmol), and tris(dibenzylideneacetone)dipalladium(0) (8 mg, 0.009 mmol) in anhydrous toluene (3 ml) was purged with N_2 for 5 min. The mixture was heated to 80 °C in a sealed tube for 18 h. The mixture was cooled, diluted with Et_2O (20 ml) and CH_2Cl_2 (20 ml), and filtered. After evaporation of the filtrate, the crude product was purified by PTLC (1.5:98.5 CH_3OH/CH_2Cl_2) to give an oil (127 mg, 93%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H), 8.13 (d, 1H, *J*=1.6 Hz), 8.06 (s, 1H), 7.97 (m, 1H), 7.77 (m, 2H), 7.5-7.2 (m, 10H), 7.15 (m, 2H), 5.06 (s, 2H), 3.52 (t, 2H, *J*=8 Hz), 0.90 (t, 2H, *J*=8 Hz), 0.03 (s, 9H).

Step 6:



A solution of the product of Step 5 (127.4 mg, 0.213 mmol), sodium acetate (43 mg, 0.52 mmol), and $H_2NOH{\cdot}HCl$ (29 mg, 0.42 mmol) in CH_3OH (3 ml) was stirred for 40 min. The solution was partitioned between 0.1 M aqueous NaOH (30 ml) and CH_2Cl_2 (50 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. PTLC (2:98 CH_3OH/CH_2Cl_2) gave a solid (82 mg, 89%).
^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, 1H, *J*=2 Hz), 8.16 (d, 1H, *J*=2.8 Hz), 8.09 (s, 1H), 8.00 (m, 1H), 7.49 (m, 4H), 5.32 (s, 2H), 3.87 (bs, 2H), 3.62 (t, 2H, *J*=8 Hz), 0.95 (t, 2H, *J*=8 Hz), 0.00 (s, 9H).

Step 7:

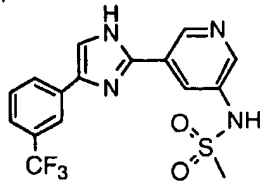


A solution of the product of Step 6 (37 mg, 0.085 mmol), ethanesulfonyl chloride (13 mg, 0.10 mmol), and pyridine (0.1 ml, 1.2 mmol) in anhydrous CH_2Cl_2 (5 ml) was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with water (20 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. PTLC (5:95 CH_3OH/CH_2Cl_2) gave an oil (28 mg, 63%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (bs, 1H), 8.53 (bs, 1H), 8.14 (s, 1H), 8.05 (s, 1H), 7.99 (m, 2H), 7.48 (m, 3H), 5.30 (s, 2H), 3.64 (t, 2H, *J*=8.4 Hz), 3.20 (q, 2H, *J*=7.2 Hz), 1.39 (t, 3H, *J*=7.2 Hz), 0.97(t, 2H, *J*=8.4 Hz), 0.02 (s, 9H).

Step 8:

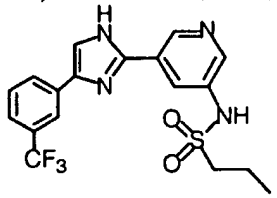
Reaction of the product of Step 7 (28 mg, 0.053 mmol) with 5 N aqueous HCl by the procedure of Example 5, Step 4, gave the product (10.5 mg, 49%). ^1H NMR (CD_3OD, 400 MHz): δ 8.70 (bs, 1H), 8.43 (bs, 1H), 8.00 (t, 1H, *J*=2 Hz), 7.94 (s, 1H), 7.86 (m, 1H), 7.45 (m, 2H), 7.40 (s, 1H), 3.10 (q, 2H, *J*=7.2 Hz), 1.31 (t, 3H, *J*=7.2 Hz). MS (CI) m/e 397 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



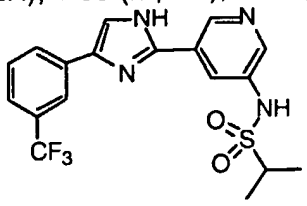
7A

^1H NMR (CD_3OD, 400 MHz): δ 8.90 (bs, 1H), 8.45 (bs, 1H), 8.29 (s, 1H), 8.15 (s, 1H), 8.07 (d, 1H, J=7.6 z), (bs, 1H, 7.6 (m, 2H), 3.13 (s, 3H). MS (ES) m/e 383.1 $(M+H)^+$.



7B

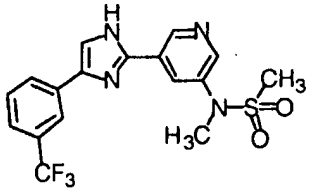
1H NMR (CD_3OD, 400 MHz): δ 8.84 (bs, 1H), 8.42 (bs, 1H), 8.26 (m, 1H), 8.14 (s, 1H), 8.05 (d, 1H, *J*=6.4 Hz), 7.75 (bs, 1H), 7.59 (m, 2H), 3.23 (m, 2H), 1.86 (m, 2H), 1.05 (t, 3H, *J*=7.2 Hz). MS (ES) m/e 411.1 $(M+H)^+$.



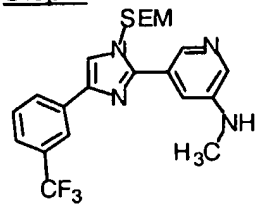
7C

1H NMR (CD_3OD, 400 MHz): δ 8.83 (bs, 1H), 8.45 (bs, 1H), 8.28 (m, 1H), 8.14 (s, 1H), 8.06 (d, 1H, *J*=7.6 Hz), 7.75 (bs, 1H), 7.59 (m, 2H), 3.43 (sept, 1H, *J*=6.8 Hz), 1.40 (d, 6H, *J*=6.8 Hz). MS (ES) m/e 411.1 $(M+H)^+$.

Example 8

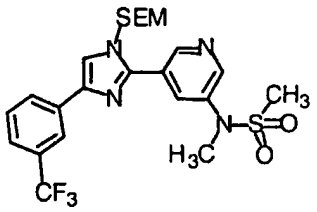


Step 1:



A mixture of the product of Example 7, Step 4 (146 mg, 0.29 mmol), palladium acetate (16 mg, 0.07 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (67 mg, 0.11 mmol), and Cs_2CO_3 (320 mg, 0.98 mmol) in toluene (3 ml) was purged with N_2 for 10 min. CH_3NH_2 (2 M in THF, 4 ml) was added, and the reaction mixture was heated at 80 °C in a sealed tube for 16 h. The reaction mixture was allowed to cool, diluted with CH_2Cl_2 (60 ml), and filtered. The filtrate was washed with H_2O (20 ml), dried ($MgSO_4$), filtered and concentrated. The residue was subjected to PTLC (5:95 CH_3OH/CH_2Cl_2) to give the product (47 mg, 36%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.33 (1H, s), 8.10 (2H, m), 8.00 (1H, m), 7.48 (3H, m), 7.36 (1H, s), 5.31 (2H, s), 4.11 (1H, bs), 3.59 (2H, t, *J*=8 Hz), 2.91 (3H, s), 0.93 (2H, t, *J*=8 Hz), -0.02 (9H, s).

Step 2:



A mixture of the product of Step 1 (16 mg, 0.04 mmol), CH_3SO_2Cl (24 mg, 0.21 mmol), and pyridine (0.07 ml, 0.9 mmol) in CH_2Cl_2 (2.5 ml) was stirred for 4 days. The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with 1N NaOH (10 ml) and H_2O (20 ml), dried ($MgSO_4$), filtered and concentrated. PTLC of the residue (5:95 CH_3OH/CH_2Cl_2) gave the product (16 mg, 75%).

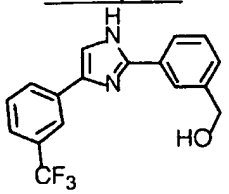
^1H NMR ($CDCl_3$, 400 MHz): δ 9.04 (1H, s), 8.72 (1H, s), 8.27 (1H, m), 8.08 (1H, s), 8.02 (1H, m), 7.52 (3H, m), 5.32 (2H, s), 3.68 (2H, t, *J*=8 Hz), 3.42 (3H, s), 2.93 (3H, s), 0.98 (2H, t, *J*=8 Hz), 0.00 (9H, s).

Step 3:

Reaction of the product of Step 2 (16 mg, 0.03 mmol) with 5N HCl by the procedure of Example 5, Step 4 gave the product (11 mg, 93%).

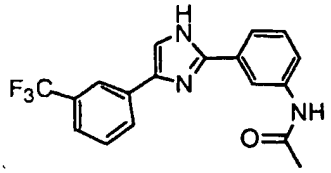
^1H NMR (CD_3OD, 400 MHz): δ 9.02 (1H, s), 8.65 (1H, m), 8.45 (1H, m), 8.15 (1H, s), 8.06 (1H, d, *J*=8 Hz), 7.77 (1H, s), 7.57 (2H, m), 3.43 (3H, s), 3.02 (3H, s). MS (ES) m/e 397 $(M+H)^+$.

Example 9



THF (1.8 ml) was added to LAH (2.5 mg, 0.066 mmol) under N_2 at 0 °C. The product of Example 1B (20 mg, 0.058 mmol) was dissolved in THF (1.4 ml) and added dropwise over 5 min. to the LAH/THF slurry. After 0.5 h, more LAH (3.8 mg, 0.10 mmol) was added and the reaction was stirred at 0 °C for 1.25 h. 10% NaOH (0.1 ml) and EtOAc (2.0 ml) was added to the reaction, followed by $MgSO_4$. The mixture was stirred, filtered and concentrated under vacuum to give the product (16 mg, 88%) as a white solid. ^1H NMR (CD_3OD, 400 MHz): δ 8.15 (bs, 1H), 8.05 (m, 1H), 7.96 (s, 1H), 7.86 (m, 1H), 7.72-7.39 (m, 5H), 4.70 (s, 2H). HRMS (FAB): Calcd for $C_{17}H_{13}N_2OF_3$ $(M+H)^+$: 319.1058. Found: 319.1059.

Example 10



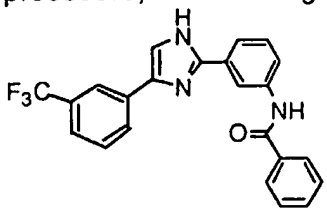
Step 1:

A solution of the product of Example 5, Step 2 (68 mg, 0.16 mmol), acetic anhydride (26 µl, 0.28 mmol) and pyridine (0.13 ml, 1.55 mmol) in CH_2Cl_2 (4 ml) was stirred for 3 days. The reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with aq. NH_4Cl (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the residue by PTLC (3:97 CH_3OH/CH_2Cl_2) gave the product (62 mg,84%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 8.00 (m, 2H), 7.85 (s, 1H), 7.77 (m, 1H), 7.49 (m, 3H), 7.40 (m, 1H), 5.33 (s, 2H), 3.61 (t, 2H, *J*=8 Hz), 2.65 (bs, 1H), 2.11 (s, 3H), 0.94 (t, 2H, *J*=8 Hz), 0.01 (s, 9H).

Step 2:

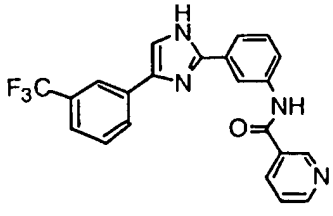
The product of Step 1 (62 mg, 0.13 mmol) and 1.0M TBAF in THF (3.0 ml, 3.0 mmol) was stirred at R.T. until no starting material remained. The reaction mixture was diluted with CH_2Cl_2 and washed with water several times, dried (K_2CO_3), filtered and evaporated. PTLC (2:98 CH_3OH/CH_2Cl_2) gave the product (37 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.85 (d, 1H, *J*=7.2 Hz), 7.55 (d, 1H, *J*=8.0 Hz), 7.42 (m, 2H), 7.32 (s, 1H), 7.29 (d, 1H, *J*=8.4 Hz), 7.19 (t, 1H, *J*=7.6 Hz), 2.10 (s, 3H). MS (FAB) m/e 364 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



10A

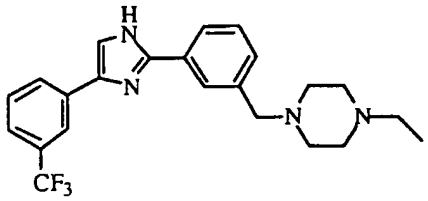
MS (CI) m/e 408 $(M+H)^+$.



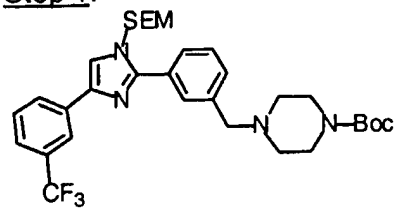
10B

MS (CI) m/e409 $(M+H)^+$.

Example 11

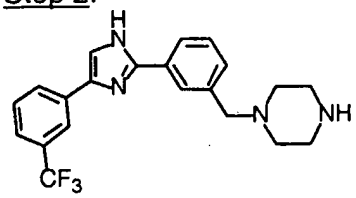


Step 1:



A mixture of the product of Example 4, Step 1 (759 mg, 1.70 mmol), *tert*-butyl 1-piperazine carboxylate (356 mg, 1.91 mmol), and sodium triacetoxyborohydride (565 mg, 2.67 mmol) in dichloroethane (9 ml) was stirred at R.T. overnight. The mixture was diluted with CH_2Cl_2 (100 ml) and washed with 1N aqueous NaOH (20 ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by flash chromatography (gradient; $CH_2Cl_2$to 1.5:98.5 CH_3OH/ CH_2Cl_2) afforded the product (902 mg, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (1H, s), 8.00 (1H, m), 7.76 (1H, bs), 7.69 (1H, m), 7.23–7.48 (5H, m), 5.29 (2H, s), 3.58 (4H, m), 3.42 (4H, bm), 2.40 (4H, bm), 1.43 (9H, s), 0.92 (2H, t, *J*=8 Hz), -0.02 (9H, s). MS *m/e* 617 $(M+H)^+$.

Step 2:



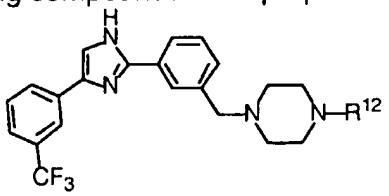
A solution of the product of Step 1 (701 mg, 1.14 mmol) in CH_3OH (5 ml) and 5N aqueous HCl (10 ml) was refluxed for 8 h. The reaction mixture was allowed to cool, then partitioned between CH_2Cl_2 (60 ml) and aqueous NH_4OH (20 ml). The aqueous layer was extracted with CH_2Cl_2 (40 ml) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Purification of the residue by flash chromatography (gradient; 5:95 to 8:92 2.0 M NH_3 in CH_3OH/ CH_2Cl_2) afforded the product

(451 mg, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (1H, s), 8.04 (1H, d, *J*=7.6 Hz), 7.94 (1H, s), 7.86 (1H, d, *J*=7.6 Hz), 7.66 (1H, s), 7.57 (2H, m), 7.44 (2H, m), 3.61 (2H, s), 2.87 (4H, t, *J*=5 Hz), 2.51 (4H, bm). MS *m/e* 387 $(M+H)^+$.

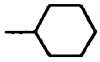
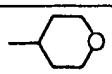
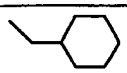
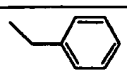
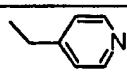
Step 3:

A mixture of the product of Step 2 (12 mg, 0.031 mmol), 1.0 M acetaldehyde in dichloroethane (33 μL, 0.033 mmol), and sodium triacetoxyborohydride (15 mg, 0.071 mmol) in dichloroethane (2 ml) was stirred overnight. The mixture was evaporated to dryness and the residue was purified by PTLC (5:95 2M NH_3 in CH_3OH/CH_2Cl_2) to give the product (8.4 mg, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (1H, s), 8.04 (1H, d, *J*=7.6 Hz), 7.93 (1H, s), 7.86 (1H, d, *J*=7.6 Hz), 7.65 (1H, bs), 7.56 (2H, m), 7.44 (2H, m), 3.62 (2H, s), 2.57 (8H, bm), 2.46 (2H, q, *J*=7.6 Hz), 1.09 (3H, t, *J*=7.6 Hz). MS *m/e* 415 $(M+H)^+$.

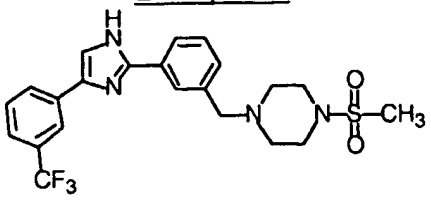
By using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



wherein R^{12} is as defined in the following table:

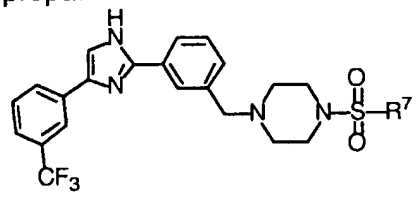
Ex.	R^{12}	$(M+H)^+$
11A		429
11B		455
11C		469
11D		471
11E		483
11F		477
11G		478

Example 12

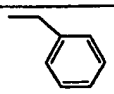
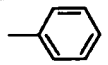
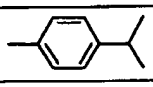


A solution of the product of Example 11, Step 2 (15 mg, 0.039 mmol), CH_3SO_2Cl (5 mg, 0.04 mmol), and pyridine (6 mg, 0.08 mmol) in CH_2Cl_2 (2.5 ml) was stirred overnight. The mixture was diluted with CH_2Cl_2 (30 ml) and washed with aqueous 1N NaOH (10 ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by TLC (5:95 2M NH_3 in CH_3OH/ CH_2Cl_2) gave the product (14 mg, 79%). ^1H NMR (400 MHz, CD_3OD) δ 8.14 (1H, s), 8.04 (1H, d, *J*=7.2 Hz), 7.96 (1H, s), 7.85 (1H, d, *J*=7.2 Hz), 7.66 (1H, s), 7.56 (2H, m), 7.43 (2H, m), 3.66 (2H, s), 3.25 (4H, m), 2.83 (3H, s), 2.61 (4H, m). MS *m/e* 465 $(M+H)^+$.

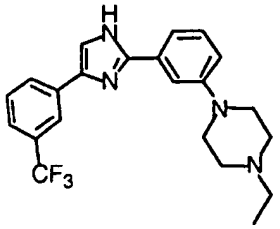
By using the appropriate sulfonyl chloride and essentially the same procedure as described in Example 12, the following compounds were prepared:



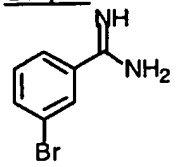
wherein R^7 is as defined in the following table:

Ex.	R^7	$(M+H)^+$
12A		479
12B		493
12C		541
12D		527
12E		569

Example 13

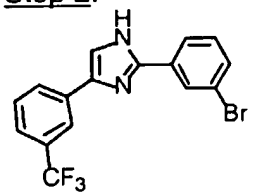


Step 1:



To a stirred, ice-cold solution of 3-bromobenzonitrile (6.0 g, 33 mmol) in THF (20 ml) was added a solution of lithium bistrimethylsilyl-amide in THF (1.0 M; 34.5 ml, 34.5 mmol). The reaction mixture was allowed to attain R.T., stirred for 16 h, then evaporated to dryness. The residue was partitioned between 9:1 $CHCl_3/CH_3OH$ (50 ml) and 10% NaOH (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated to give the product (7.2 g). ^1H NMR (400 MHz, CD_3OD) δ 7.92 (1H, t, J=2 Hz), 7.72 (2H, m), 7.40 (1H, t, J=8 Hz).

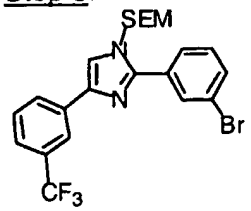
Step 2:



A mixture of Preparation 1 (3.8 g, 14 mmol), the product of Step 1 (7.2 g), and Na_2CO_3 (2.96 g, 27.9 mmol) in DMF (60 ml) was stirred for 16 h. The reaction mixture was concentrated, the residue was taken up in CH_2Cl_2 (150 ml), and washed with water (3x100 ml). The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was subjected to flash chromatography (3:2 EtOAc/hexanes) to give the product as a solid (4.74 g, 91%).

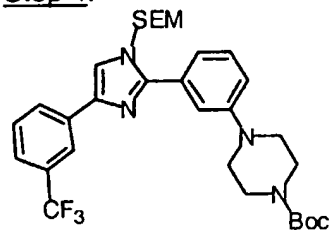
^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, bs), 8.00 (1H, s), 7.93 (2H, m), 7.71 (1H, d, J=8 Hz), 7.43 (4H, m), 7.19 (1H, t, J=8 Hz).

Step 3:



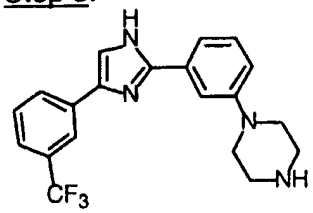
By using the procedure of Preparation 2, Step 2, the product of Step 2 (4.74 g, 12.9 mmol) was reacted with (2-trimethylsilyl)ethoxymethyl chloride (2.7 ml, 15 mmol) to give the product (5.31 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, s), 8.02 (2H, m), 7.79 (1H, d, *J*=7.2 Hz), 7.58 (1H, d, *J*=8.8 Hz), 7.48 (3H, m), 7.35 (1H, t, *J*=7.8 Hz), 5.29 (2H, s), 3.63 (2H, t, *J*=8.3 Hz), 0.96 (2H, t, *J*=8.3 Hz), -0.01 (9H, s). MS *m/e* 499 $(M+H)^+$.

Step 4:



A mixture of the product of Step 3 (1.275 g, 2.56 mmol), palladium acetate (63 mg, 0.28 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (328 mg, 0.52 mmol), (N-tert-butoxycarbonyl)piperazine (1.025 g, 5.503 mmol), and Cs_2CO_3 (2.53 g, 7.75 mmol) in toluene (35 ml) was purged with N_2 for 10 min, then heated at 80 °C for 16 h. The reaction mixture was allowed to cool, solids were removed by filtration, and the filtrate was concentrated. The residue was partitioned between H_2O (50 ml) and CH_2Cl_2 (100 ml), and the organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (1:9 EtOAc/hexanes) to give the product (1.07 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, s), 8.02 (1H, bs), 7.47 (3H, m), 7.35 (2H, m), 7.26 (1H, m), 7.00 (1H, m), 5.30 (2H, s), 3.57 (6H, m), 3.20 (4H, m), 1.46 (9H, s), 0.92 (2H, m), -0.03 (9H, s). MS *m/e* 603 $(M+H)^+$.

Step 5:

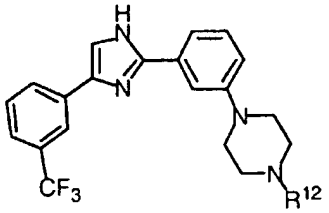


Reaction of the product of Step 4 (1.07 g, 1.78 mmol) with 5 N HCl by the procedure of Example 11, Step 2 gave the product (584 mg, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (1H, s), 8.03 (1H, d, *J*=7.6 Hz), 7.63 (1H, s), 7.56 (3H, m), 7.40 (1H, m), 7.34 (1H, t, *J*=7.8 Hz), 7.01 (1H, m), 3.23 (4H, m), 3.00 (4H, m). MS *m/e* 373 $(M+H)^+$.

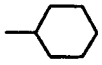
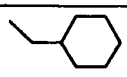
Step 6:

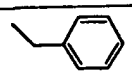
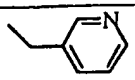
Reaction of the product of Step 5 (10 mg, 0.027 mmol) with acetaldehyde by the procedure of Example 11, Step 3 gave the product (6.6 mg, 61%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (1H, s), 8.03 (1H, d, *J*=7.6 Hz), 7.58 (4H, m), 7.40 (1H, m), 7.35 (1H, t, *J*=7.8 Hz), 7.03 (1H, m), 3.33 (4H, m), 2.70 (4H, m), 2.53 (2H, q, *J*=7.2 Hz), 1.17 (3H, t, *J*=7.2 Hz). MS *m/e* 401 $(M+H)^+$.

Using a similar procedure, the following compounds were prepared:

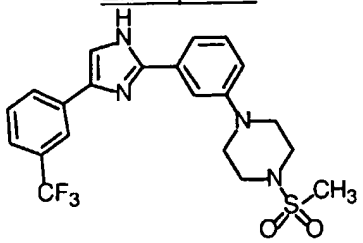


wherein R^{12} is as defined in the table

Ex.	R^{12}	$(M+H)^+$
13A	$-CH_3$	387
13B		415
13C		415
13D		455
13E		429
13F		469

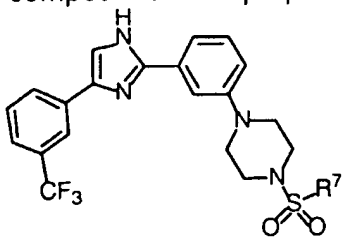
13G		463
13H		464

Example 14

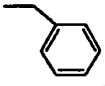


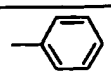
Reaction of the product of Example 13, Step 5 (15 mg, 0.040 mmol) with CH_3SO_2Cl (7.2 mg, 0.063 mmol) by the procedure of Example 12 afforded the product (15.4 mg, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.95 (1H, m), 7.57 (1H, s), 7.48 (2H, m), 7.41 (1H, s), 7.34 (1H, m), 7.27 (1H, m), 6.87 (1H, m), 3.27 (8H, m), 2.77 (3H, s). MS *m/e* 451 $(M+H)^+$.

By using the appropriate sulfonyl chloride and essentially the same procedure, the following compounds were prepared:

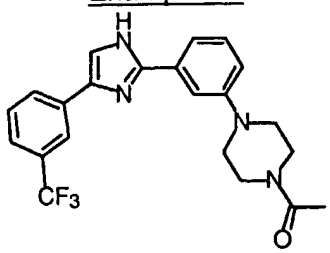


wherein R^7 is as defined in the following table:

Ex.	R^7	$(M+H)^+$
14A		465
14B		479
14C		479
14D		527

14E		513

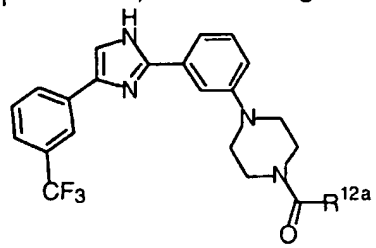
Example 15



A solution of the product of Example 13, Step 5 (12 mg, 0.032 mmol), acetic anhydride (3.6 mg, 0.035 mmol), and triethylamine (3.4 mg, 0.034 mmol) in CH_2Cl_2 (1.5 ml) was stirred overnight. Purification by TLC (1:20 CH_3OH/CH_2Cl_2) gave the product (13.4 mg, 100%).

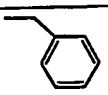
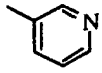
^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.97 (1H, m), 7.60 (1H, s), 7.47 (3H, m), 7.43 (1H, s), 7.28 (1H, t, *J*=8 Hz), 6.89 (1H, m), 3.73 (2H, t, *J*=5.2 Hz), 3.57 (2H, t, *J*=5 Hz), 3.19 (2H, t, *J*=5.2 Hz), 3.11 (2H, t, *J*=5 Hz), 2.08 (3H, s). MS *m/e* 415 $(M+H)^+$.

By using the appropriate acid chloride and essentially the same procedure, the following compounds were prepared:

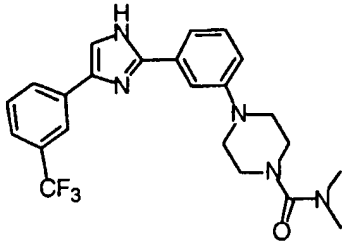


wherein R^{12a} is as defined in the following table:

Ex.	R^{12a}	$(M+H)^+$
15A		429
15B		443
15C		443
15D		457
15E		441

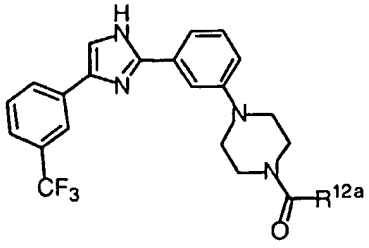
15F		483
15G		491
15H		477
15I		478

Example 16

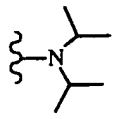
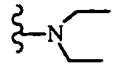


A solution of the product of Example 13, Step 5 (12 mg, 0.032 mmol), 1.0 M dimethylcarbamyl chloride in dichloroethane (0.04 ml, 0.04 mmol), and triethylamine (5 mg, 0.05 mmol) in CH_2Cl_2 (1.5 ml) was stirred overnight. Purification by TLC (1:20 CH_3OH/CH_2Cl_2) gave the product (10.6 mg, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, s), 7.93 (1H, m), 7.52 (1H, s), 7.44 (2H, m), 7.41 (1H, s), 7.37 (1H, d, *J*=7.6 Hz), 7.24 (1H, t, *J*=7.2 Hz), 6.83 (1H, m), 3.28 (4H, m), 3.06 (4H, m), 2.80 (6H, s). MS *m/e* 444 $(M+H)^+$.

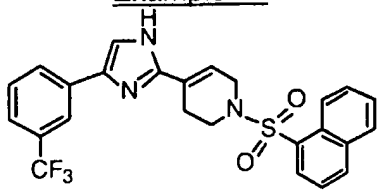
By using the appropriate carbamyl chloride and essentially the same procedure as described in Example 16, the following compounds were prepared:



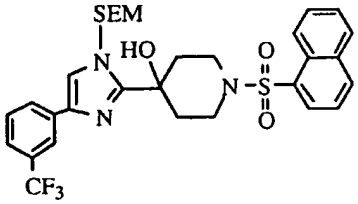
wherein R^{12a} is as defined in the following table:

Ex.	R^{12a}	$(M+H)^+$
16A		500
16B		472

Example 17



Step 1:



A solution of Preparation 2, Step 2 (0.18 g, 0.51 mmol) in THF (5 ml) under N_2 was cooled to -78 °C and *n*-BuLi (0.48 ml, 0.77 mmol) was added dropwise. The reaction was stirred for 10 min., then *N*-tert-butoxycarbonyl-4-piperidone (0.11 g, 0.56 mmol) in THF (2 ml) was added dropwise. After stirring for 2.5 h, the reaction was quenched with water, extracted with EtOAc, dried over K_2CO_3, filtered and concentrated under vacuum to give a residue (0.28 g, 100%) which was used in the next reaction without further purification.

To solution of the residue (0.28 g, 0.51 mmol) in CH_2Cl_2 (7 ml) under N_2 was added TFA (0.6 ml). After stirring at R.T. for 40 min., the reaction was washed with water, treated with 1 N NaOH, extracted with CH_2Cl_2, dried over K_2CO_3, filtered and concentrated under vacuum to give the residue (0.19 g, 80%) which was used in the next reaction without further purification.

The residue (0.13 g, 0.29 mmol) was dissolved in CH_2Cl_2 (3 ml) under N_2 and Et_3N (80 μL, 0.58 mmol) was added, followed by the dropwise addition of 1-naphthalenesulfonyl chloride (0.079 g, 0.34 mmol) in CH_2Cl_2 (1 ml). After stirring at R.T. for 18 h, the reaction was treated

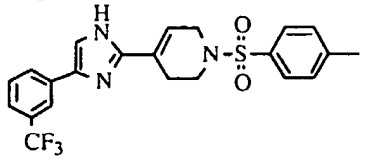
with 1 N NaOH, extracted with CH_2Cl_2, dried over K_2CO_3, filtered and concentrated under vacuum. Purification via PTLC (40:60 EtOAc/ hexanes) yielded the product (0.15 g, 84%). MS (CI) *m/e* 632 $(M+H)^+$.

Step 2:

To solution of the product of Step 1 (0.15 g, 0.24 mmol) in CH_3OH (4.5 ml) under N_2 was added HCl (6 N in CH_3OH, 4 ml). The reaction was heated to 80 °C in a sealed tube. After stirring for 15 min., the reaction was treated with 1 N NaOH, extracted with CH_2Cl_2, dried over K_2CO_3, filtered and concentrated under vacuum to yield the free imidazole (0.092 g, 77%) which was used in the next reaction without further purification.

The imidazole (0.092 g, 0.18 mmol) in AcOH (3 ml) and Ac_2O (90 μL, 0.90 mmol) was heated to 140 °C. After 2.25 h, the AcOH was evaporated off and water was added, followed by a few drops of EtOAc. The mixture was stirred for a few minutes, then basified with K_2CO_3, extracted with EtOAc, dried over K_2CO_3 and concentrated under vacuum. The residue was subjected to PTLC (4:96 2 M NH_3 in CH_3OH/ CH_2Cl_2) to yield the product (0.059 g, 68%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, 1H, *J*=8.8 Hz), 8.30 (dd, 1H, *J*=1.2, 7.4 Hz), 8.14 (d, 1H, *J*=8.2 Hz), 8.03-7.91 (m, 3H), 7.73–7.58 (m, 3H), 7.54–7.46 (m, 2H), 7.35 (s, 1H), 6.41 (bs, 1H), 4.00 (m, 2H), 3.56 (t, 2H, *J*=5.7 Hz), 2.79 (m, 2H). HRMS: Calc'd for $C_{25}H_{20}N_3O_2SF_3$ $(M+H)^+$: 484.1307. Found: 484.1317.

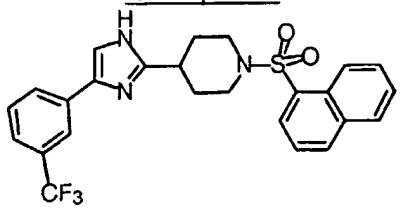
Using appropriate starting materials and essentially the same procedure, the following compound was prepared:



17A

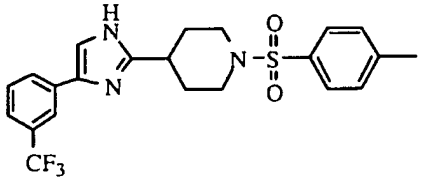
HRMS: Calc'd for $C_{22}H_{20}N_3O_2SF_3$ $(M+H)^+$: 448.1307. Found: 448.1308.

Example 18



To a solution of Example 17 (0.037 g, 0.077 mmol) in EtOH (2.5 ml) was added 10% Pd/C. The mixture was stirred under a balloon of H_2 for 16 h, then filtered through celite, and the filter pad was washed with EtOH. The combined filtrate and washings were concentrated under vacuum. The residue was subjected to PTLC (4:96 2 M NH_3 in CH_3OH/CH_2Cl_2) to yield the product (0.019 g, 50%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, 1H, *J*=8.8 Hz), 8.27 (dd, 1H, *J*=1.2, 7.4 Hz), 8.14 (d, 1H, *J*=8.2 Hz), 8.03-7.92 (m, 2H), 7.86 (bd, 1H, *J*=7.0 Hz), 7.74-7.58 (m, 3H), 7.51-7.42 (m, 2H), 7.30 (s, 1H), 4.01 (m, 2H), 2.90 (m, 2H), 2.78 (m, 2H), 2.20-2.08 (m, 2H), 2.01-1.86 (m, 2H). HRMS: Calc'd for $C_{25}H_{22}N_3O_2SF_3$ $(M+H)^+$: 486.1463. Found: 486.1466.

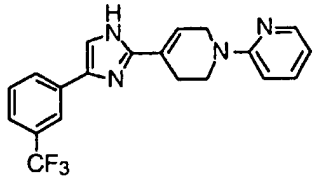
Using appropriate starting materials and essentially the same procedure, the following compound was prepared:



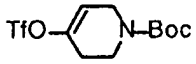
18A

HRMS: Calcd for $C_{22}H_{22}N_3O_2SF_3$ $(M+H)^+$: 450.1463. Found: 450.1457.

Example 19



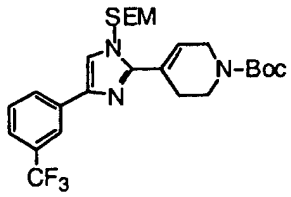
Step 1:



A solution of 1-Boc-4-piperidone (2.629 g, 13.19 mmol) in THF (7.5 ml) was added dropwise to freshly prepared LDA (9.3 ml of 1.6 M butyllithium in hexanes and 1.54 g diisopropylamine) in THF (15 ml) in a dry ice-acetone bath. After 1 h a solution of N-phenyltrifluoromethane-sulfonimide (4.851 g, 13.58 mmol) in THF (10 ml) was added and the solution was allowed to warm up to 0°C and stirred in an ice-water bath for 4 h. The volatiles were evaporated and the residue was subjected to a

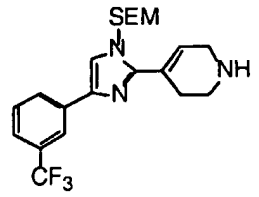
flash column (neutral alumina, hexanes, then gradient of increasing EtOAc concentration to 4:96 EtOAc/hexanes) to give the product (1.440 g, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, b), 4.02 (2H, m), 3.61 (2H, m), 2.42 (2H, m), 1.45 (9H, s).

Step 2:



To a solution of the product of Preparation 2, Step 2 (359 mg, 1.05 mmol) in THF (5 ml) in a dry ice-acetone bath was added 1.6 M butyllithium in hexanes (0.80 ml, 1.3 mmol). The solution was stirred for 15 min. then zinc chloride (442 mg, 3.25 mmol) in THF (3 ml) was added. The mixture was stirred at –78°C for 10 min. and warmed to R.T. over 30 min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium dichloride (68 mg, 0.083 mmol) and the product of Step 1 (480 mg, 1.45 mmol) were added. The mixture was purged with nitrogen for 5 min. and then heated at 90°C for 16 h. The reaction mixture was cooled down and poured into 10% aqueous NH_4OH (50 ml). The whole was extracted with CH_2Cl_2 (2x50 ml), dried ($MgSO_4$), concentrated, and purified by PTLC (1:4 EtOAc/ hexanes) to give the product (114 mg, 21%). MS (ES) *m/e* 524 $(M+H)^+$.

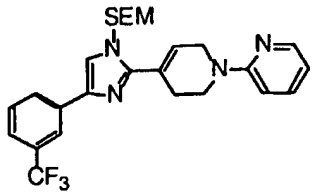
Step 3:



A solution of the product of Step 2 (114 mg, 0.218 mmol) in 10% TFA/CH_2Cl_2 (5 ml) was stirred in an ice-water bath for 10 min. then at R.T. for 2 h. The solution was partitioned between CH_2Cl_2 (30 ml) and 1N NaOH (20 ml). The aqueous layer was extracted again with CH_2Cl_2 (20 ml) and the combined organic layer was dried over $MgSO_4$. The crude

mixture after concentration was subjected to PTLC (8:92 2M NH_3-MeOH/ CH_2Cl_2) to give the product (67 mg, 73%). MS (ES) *m/e* 424 $(M+H)^+$.

Step 4:

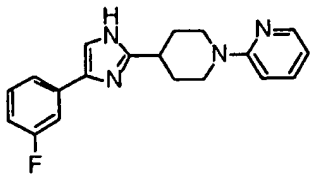


A mixture of the product of Step 3 (67 mg, 0.16 mmol), 2-bromo-pyridine (61 mg, 0.38 mmol), sodium *t*-butoxide (53 mg, 0.55 mmol), bis(diphenylphosphino)propane (16 mg, 0.039 mmol), and palladium(II) acetate (7 mg, 0.03 mmol) in toluene (4 ml) was heated at 100°C in a sealed vessel for 16 h. The mixture was diluted with CH_2Cl_2 (40 ml) and filtered. The filtrate was evaporated to dryness and subjected to PTLC (3:97 MeOH/CH_2Cl_2) to give the product (36 mg, 45%). MS (ES) *m/e* 501 $(M+H)^+$.

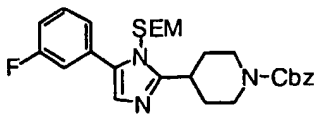
Step 5:

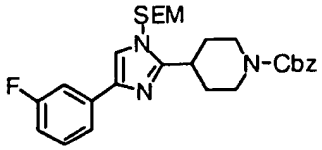
Reaction of the product of Step 4 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the product (13 mg, 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, m), 7.99 (1H, s), 7.90 (1H, m), 7.53 (1H, m), 7.47 (2H, m), 7.34 (1H, s), 6.68 (1H, m), 6.63 (1H, m), 6.51 (1H, m), 4.17 (2H, m), 3.83 (2H, m), 2.79 (2H, m). MS (ES) *m/e* 371 $(M+H)^+$.

Example 20



Step 1:

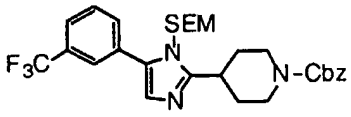


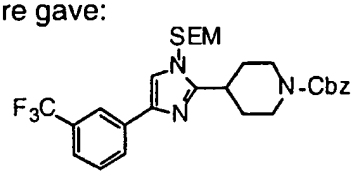


20-1-1

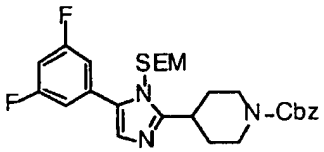
A mixture of Preparation 3 (0.693 g, 1.40 mmol), 3-fluorophenylboronic acid (0.410 g, 2.93 mmol), potassium phosphate (0.650 g, 3.07 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.064 g, 0.078 mmol) in DME (5 ml) was heated at 80°C in a sealed vessel for 16 h. The mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The filtrate was washed with water (30 ml), dried ($MgSO_4$), concentrated, and purified by PTLC (2.5:97.5 MeOH/CH_2Cl_2) to give isomer A (0.214 g, 30%) and isomer B (0.263 g, 37%). MS (ES) *m/e* 510 $(M+H)^+$.

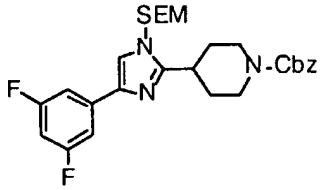
Coupling of Preparation 3 with the appropriate boronic acids by essentially the same procedure gave:



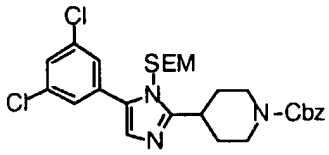


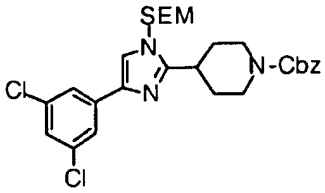
20-1-2 MS (ES) *m/e* 560 $(M+H)^+$.





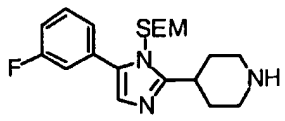
20-1-3 MS (ES) *m/e* 528 $(M+H)^+$.

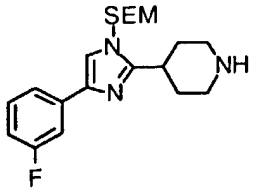




20-1-4 MS (ES) *m/e* 560 $(M+H)^+$.

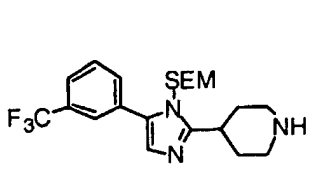
Step 2:

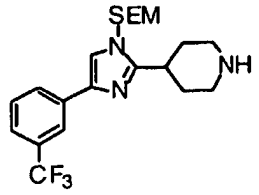




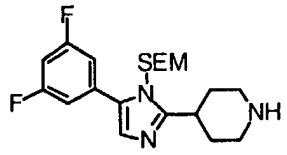
20-2-1

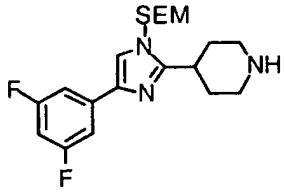
A mixture of 20-1-1 (0.214 g, 0.421 mmol) and 10% Pd/C (0.023 g) in EtOH (8 ml) was stirred under H_2 (1 atm) for 16 h. The mixture was filtered and the filtrate was evaporated to dryness to give the product (0.158 g, 100%). MS (ES) *m/e* 376 $(M+H)^+$.





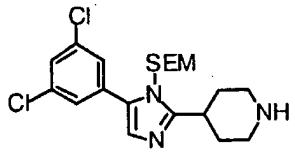
20-2-2 MS (ES) *m/e* 426 $(M+H)^+$.

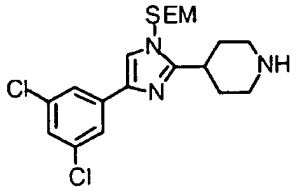




20-2-3 MS (ES) *m/e* 394 $(M+H)^+$

Additional piperidine derivatives were prepared from 20-1-4 according to the following procedure.

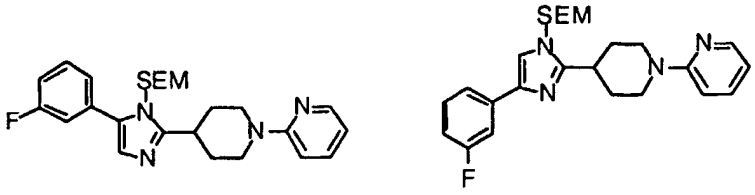




20-2-4

A mixture of 20-1-4 (179 mg, 0.319 mmol), 50% aq. KOH (6 ml), and EtOH (6 ml) was heated at 100°C for 3 h. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (50 ml) and water (20 ml). The aqueous layer was washed with CH_2Cl_2 (20 ml). The combined organic layer was dried (Na_2SO_4) and concentrated to give the product (164 mg), which was used without further purification. MS (ES) *m/e* 426 $(M+H)^+$.

Step 3:



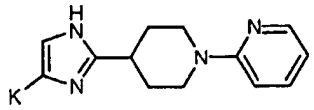
20-3-1

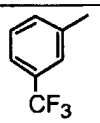
A mixture of 20-2-1 (81 mg, 0.21 mmol), 2-bromopyridine (88 mg, 0.56 mmol), palladium(II) acetate (10 mg, 0.045 mmol), bis(diphenylphosphino)propane (26 mg, 0.063 mmol), and sodium *t*-butoxide (88 mg, 0.92 mmol) in anhydrous toluene (4 ml) was heated at 110°C in a sealed vessel for 16 h. The mixture was diluted with CH_2Cl_2 (40 ml) and filtered. The filtrate was evaporated to dryness and purified by PTLC (2:98 MeOH/CH_2Cl_2) to give the product (58 mg, 61%). MS (ES) *m/e* 453 $(M+H)^+$.

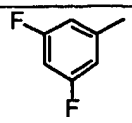
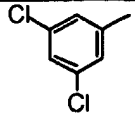
Step 4:

Reaction of 20-3-1 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the product (43 mg, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 (1H, m), 7.45 (3H, m), 7.28 (1H, m), 7.19 (1H, s), 6.88 (1H, m), 6.67 (1H, m), 6.59 (1H, m), 4.35 (2H, m), 3.04 (1H, m), 2.95 (2H, m), 2.11 (2H, m), 1.81 (2H, m). MS (ES) *m/e* 323 $(M+H)^+$.

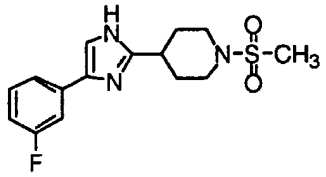
The following examples were prepared from the corresponding products of Step 2 using essentially the same procedures described in Step 3 and Step 4:



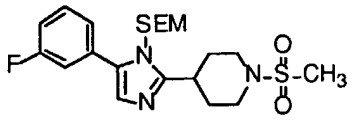
Ex.	K	$(M+H)^+$
20A		373

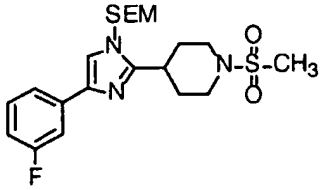
20B		341
20C		373

Example 21



Step 1:



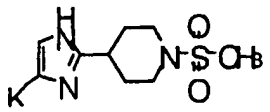


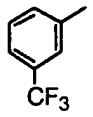
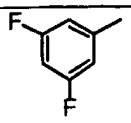
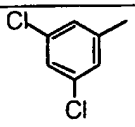
A solution of 20-2-1 (40 mg, 0.11 mmol), methanesulfonyl chloride (14 mg, 0.12 mmol), and triethylamine (20 mg, 0.20 mmol) in CH_2Cl_2 (4 ml) was stirred at R.T. for 16 h. The mixture was diluted with CH_2Cl_2 (40 ml) and washed with 1N NaOH (10 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (2:98 MeOH/CH_2Cl_2) to give the product (34 mg, 68%). MS (ES) *m/e* 454 $(M+H)^+$.

Step 2:

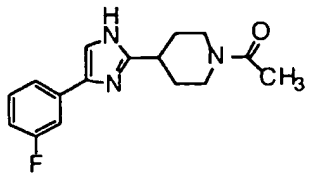
Reaction of the product of Step 1 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the product (23 mg, 96%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, m), 7.29 (1H, m), 7.22 (1H, s), 6.90 (1H, m), 3.86 (2H, m), 2.96 (1H, m), 2.82 (5H, m), 2.14 (2H, m), 1.91 (2H, m). MS (ES) *m/e* 324 $(M+H)^+$.

The following examples were prepared from the corresponding products of Example 20, Step 2 using essentially the same procedures described in Step 1 and Step 2:

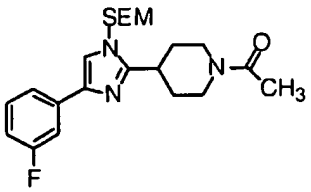


Ex.	K	$(M+H)^+$
21A		374
21B		342
21C		374

Example 22



Step 1:

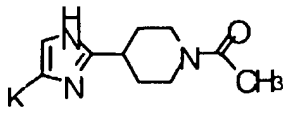


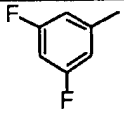
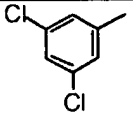
A solution of 20-2-1 (40 mg, 0.11 mmol), acetic anhydride (12 mg, 0.12 mmol), and triethylamine (24 mg, 0.24 mmol) in CH_2Cl_2 (4 ml) was stirred at R.T. for 16 h. The mixture was diluted with CH_2Cl_2 (40 ml) and washed with 1N NaOH (10 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (2:98 MeOH/CH_2Cl_2) to give the product (30 mg, 69%). MS (ES) *m/e* 418 $(M+H)^+$.

Step 2:

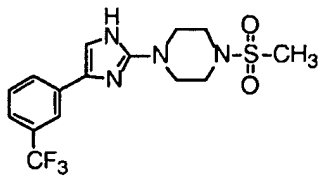
A solution of the product of Step 1 (30 mg, 0.072 mmol) in MeOH (1 ml) and 5N HCl (3 ml) was refluxed for 4 h. The mixture was partitioned between CH_2Cl_2 (30 ml) and aqueous NH_4OH (15 ml). The organic layer was concentrated and the residue was reacted with acetic anhydride (8 mg, 0.08 mmol) in CH_2Cl_2 (5 ml) at R.T. for 16 h. The mixture was diluted with CH_2Cl_2 (30 ml) and washed with 1N NaOH (10 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (5:95 MeOH/CH_2Cl_2) to give the product (14 mg, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, m), 7.29 (1H, m), 7.23 (1H, s), 6.88 (1H, m), 4.66 (1H, m), 3.91 (1H, m), 3.21 (1H, m), 3.09 (1H, m), 2.73 (1H, m), 2.14 (1H, m), 2.11 (3H, s), 2.01 (1H, m), 1.74 (2H, m). MS (ES) *m/e* 288 $(M+H)^+$.

The following examples were prepared from the corresponding products of Example 20, Step 2 using essentially the same procedures described in Step 1 and Step 2:

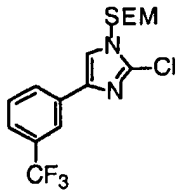


Ex.	K	$(M+H)^+$
22A		306
22B		338

Example 23

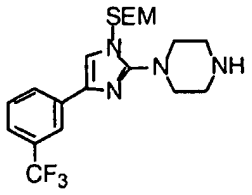


Step 1:



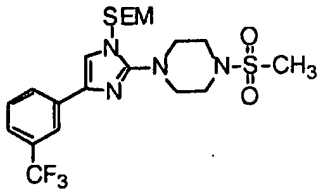
To a solution of Preparation 2 (8.734 g, 18.65 mmol) in anhydrous THF (35 ml) at –78°C was added 2.5 M butyllithium in hexanes (9.50 ml, 23.8 mmol). The solution was stirred at –78°C for 40 min and a solution of hexachloroethane (9.69 g, 40.9 mmol) in THF (25 ml) was added through a cannular. The resulting solution was allowed to warm to R.T. and stirred for 16 h. The solution was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (300 ml) and water (200 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography (hexanes, then gradient of increasing EtOAc concentration to 4:96 EtOAc/hexanes) to give the product (6.189 g, 88%). MS (ES) *m/e* 377 $(M+H)^+$.

Step 2:



A mixture of the product of Step 1 (5.142 g, 13.64 mmol), piperazine (53.06 g, 615.9 mmol), copper(II) sulfate (9.05 g, 56.7 mmol) in diglyme (10 ml) was heated to 170°C for 48 h in a sealed vessel. The reaction mixture was cooled to R.T. and treated with CH_2Cl_2 (600 ml). The mixture was filtered and the filtrate was washed with water (2x350 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography (CH_2Cl_2, then gradient of increasing MeOH concentration to 1:9 MeOH/CH_2Cl_2) to give the product (4.116 g, 71%). MS (ES) *m/e* 427 $(M+H)^+$.

Step 3:

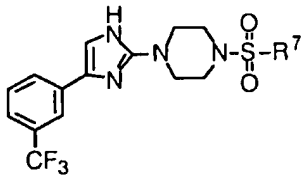


A solution of the product of Step 2 (75 mg, 0.18 mmol), methanesulfonyl chloride (29 mg, 0.26 mmol), and triethylamine (38 mg, 0.38 mmol) in CH_2Cl_2 (5 ml) was stirred at R.T. for 16 h. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with 1N NaOH (20 ml), then sat'd aq. NH_4Cl (20 ml). The organic layer was dried ($MgSO_4$), concentrated, and subjected to PTLC (2:98 MeOH/CH_2Cl_2) to give the product (73 mg, 81%). MS (ES) *m/e* 505 $(M+H)^+$.

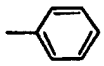
Step 4:

A solution of the product of Step 3 (73 mg, 0.14 mmol) in MeOH (3 ml) and 5N HCl (7 ml) was refluxed for 4 h. The reaction mixture was partitioned between CH_2Cl_2 (40 ml) and aq. NH_4OH (20 ml). The organic layer was dried ($MgSO_4$), concentrated, and subjected to PTLC (5:95 MeOH/CH_2Cl_2) to give the product (52 mg, 97%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, s), 7.80 (1H, m), 7.42 (2H, m), 7.04 (1H, s), 3.50 (4H, t, *J*=5 Hz), 3.34 (4H, t, *J*=5 Hz), 2.80 (3H, s). MS (ES) *m/e* 375 $(M+H)^+$.

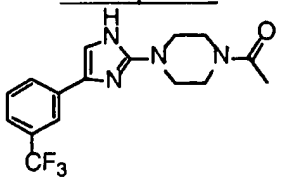
By using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



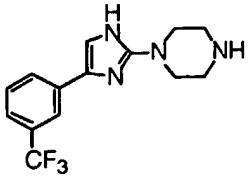
Ex.	R^7	$(M+H)^+$
23A	$-CH_2CH_3$	389
23B	$-CH_2CH_2CH_3$	403

23C		403
23D		437
23E	$-CF_3$	429

Example 24



Step 1:

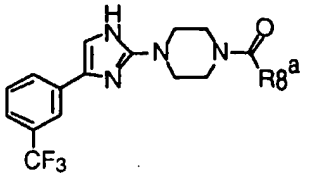


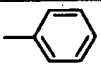
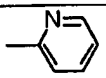
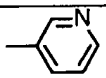
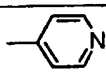
A solution of the product of Example 23, Step 2 (602 mg, 1.41 mmol) in MeOH (5 ml) and 5N HCl (9 ml) was refluxed for 3 h. The reaction mixture was partitioned between CH_2Cl_2 (3x60 ml) and aq. NH_4OH (50 ml). The organic layer was dried ($MgSO_4$), concentrated, and subjected to PTLC (16:84 2M NH_3 in $MeOH/CH_2Cl_2$) to give the product (343 mg, 82%). MS (ES) *m/e* 297 $(M+H)^+$.

Step 2:

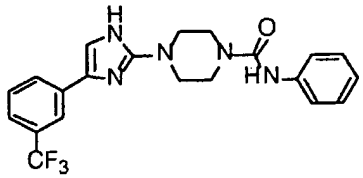
A solution of the product of Step 1 (31 mg, 0.11 mmol), acetyl chloride (8 mg, 0.1 mmol), and triethylamine (11 mg, 0.11 mmol) in CH_2Cl_2 (2 ml) was stirred at R.T. for 16 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed with water (20 ml). The organic layer was dried ($MgSO_4$), concentrated, and subjected to PTLC (5:95 $MeOH/CH_2Cl_2$) to give the product (17 mg, 47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, b), 7.85 (2H, m), 7.41 (2H, m), 7.05 (1H, s), 3.73 (2H, m), 3.60 (2H, m), 3.47 (2H, m), 3.29 (2H, m), 2.13 (3H, s). MS (ES) *m/e* 339 $(M+H)^+$.

By using appropriate starting materials and essentially the same procedure, the following compounds were prepared:



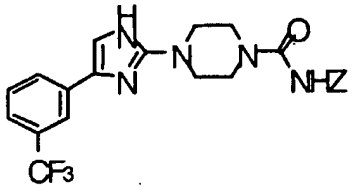
Ex.	$R8^a$	$(M+H)^+$
24A		365
24B		401
24C		402
24D		402
24E		402

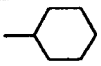
Example 25



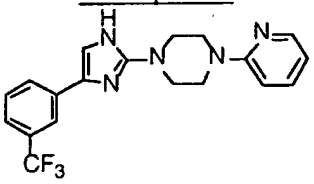
To a solution of the product of Example 24, Step 1 (31 mg, 0.10 mmol) and triethylamine (11 mg, 0.11 mmol) in CH_2Cl_2 (2 ml) was added phenylisocyanate (13 mg, 0.11 mmol) in CH_2Cl_2 (1 ml) dropwise. The mixture was stirred at R.T. for 16 h and then evaporated to dryness. The residue was purified by PTLC (5:95 MeOH/CH_2Cl_2) to give the product (23 mg, 54%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, b), 7.75 (1H, b), 7.2-7.4 (6H, m), 7.07 (1H, m), 6.72 (2H, b), 3.53 (4H, m), 3.38 (4H, m). MS (ES) *m/e* 416 $(M+H)^+$.

By using appropriate starting materials and essentially the same procedure, the following compounds were prepared:

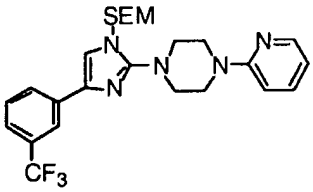


Ex.	Z	$(M+H)^+$
25A	—H	340
25B		396
25C		422

Example 26



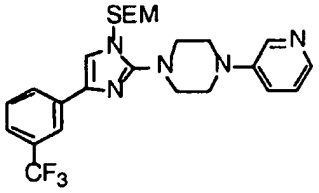
Step 1:



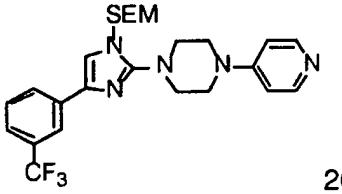
26-1-1

A mixture of the product of Example 23, Step 2 (123 mg, 0.288 mmol), palladium acetate (7 mg, 0.03 mmol), bis(diphenylphosphino)propane (10 mg, 0.024 mmol), sodium *t*-butoxide (87 mg, 0.91 mmol), and 2-bromopyridine (114 mg, 0.722 mmol) in anhydrous toluene (2.5 ml) was heated to 80°C in a sealed vessel for 16 h. The mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The filtrate was evaporated to dryness and purified by PTLC (3:97 MeOH/CH_2Cl_2) to give the product (120 mg, 83%). MS (ES) *m/e* 504 $(M+H)^+$.

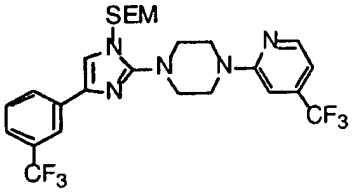
Coupling of the product of Example 23, Step 2 with the appropriate aryl or heteroaryl halides by essentially the same procedure gave:



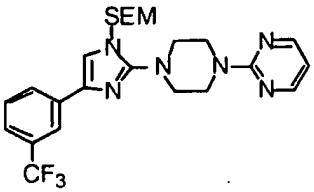
26-1-2 MS (ES) *m/e* 504 $(M+H)^+$.



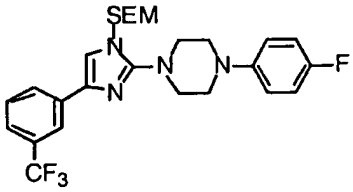
26-1-3 MS (ES) *m/e* 504 $(M+H)^+$.



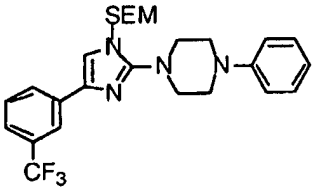
26-1-4 MS (ES) *m/e* 572 $(M+H)^+$.



26-1-5 MS (ES) *m/e* 505 $(M+H)^+$.

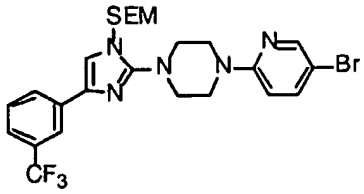


26-1-6 MS (ES) *m/e* 521 $(M+H)^+$.



26-1-7 MS (ES) *m/e* 503 $(M+H)^+$.

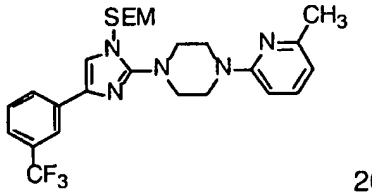
Additional (4'-aryl or 4'-heteroarylpiperazinyl)imidazoles were prepared according to the following procedure.



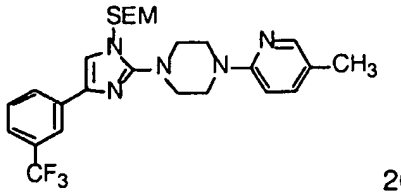
26-1-8

A mixture of the product of Example 23, Step 2 (132 mg, 0.309 mmol), 2,5-dibromopyridine (151 mg, 0.637 mmol), bis(dibenzylideneacetone)palladium (10 mg, 0.017 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (23 mg, 0.037 mmol), and sodium *t*-butoxide (85 mg, 0.88 mmol) in anhydrous toluene (2.5 ml) was heated to 110°C in a sealed vessel for 16 h. The mixture was diluted with CH_2Cl_2 (40 ml) and filtered. The filtrate was evaporated to dryness and purified by PTLC (1.5:98.5 MeOH/CH_2Cl_2) to give the product (118 mg, 65%). MS (ES) *m/e* 582. $(M+H)^+$.

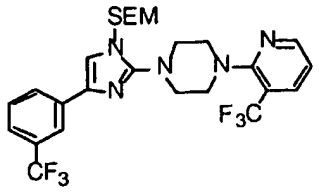
Using the appropriate aryl or heteroaryl halides and essentially the same procedure, the following compounds were prepared.



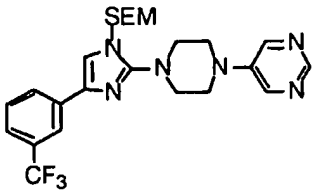
26-1-9 MS (FAB) *m/e* 518 $(M+H)^+$.



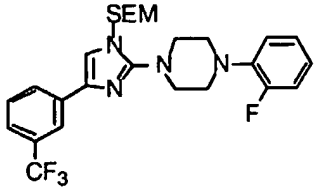
26-1-10 MS (ES) *m/e* 518 $(M+H)^+$.



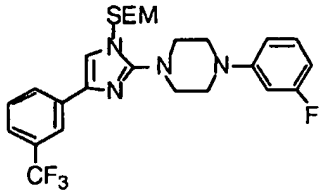
26-1-11 MS (ES) *m/e* 572 $(M+H)^+$.



26-1-12 MS (ES) *m/e* 505 $(M+H)^+$.



26-1-13 MS (ES) *m/e* 521 $(M+H)^+$.

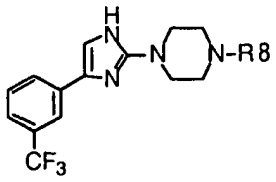


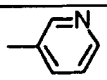
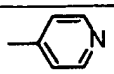
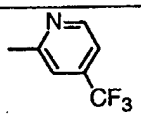
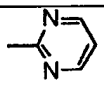
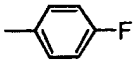
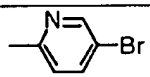
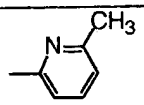
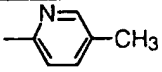
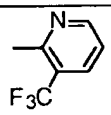
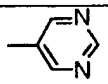
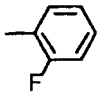
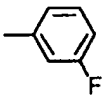
26-1-14 MS (ES) *m/e* 521 $(M+H)^+$.

Step 2:

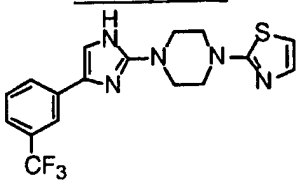
A solution of 26-1-1 (120 mg, 0.238 mmol) in MeOH (3 ml) and 5N HCl (5 ml) was refluxed for 4 h. The reaction mixture was partitioned between CH_2Cl_2 (50 ml) and aq. NH_4OH (20 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (5:95 $MeOH/CH_2Cl_2$) to give the product (89 mg, 100%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, m), 7.88 (1H, s), 7.80 (1H, m), 7.49 (1H, m), 7.40 (2H, m), 7.05 (1H, s), 6.66 (2H, m), 3.65 (4H, m), 3.48 (4H, m). MS (ES) *m/e* 374 $(M+H)^+$.

The following examples were prepared from the corresponding products of Step 1 using essentially the same procedure.

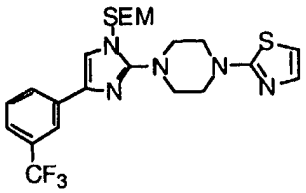


Ex.	R8	$(M+H)^+$
26A		374
26B		374
26C		442
26D		375
26E		391
26F		373
26G		452
26H		388
26I		388
26J		442
26K		375
26L		391
26M		391

Example 27



Step 1:

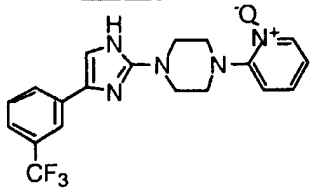


A mixture of the product of Example 23, Step 2 (107 mg, 0.251 mmol), 2-bromothiazole (93 mg, 0.57 mmol), and anhydrous potassium carbonate (98 mg, 0.71 mmol) in anhydrous DMF (2.5 ml) was heated at 160°C for 16 h. The volatiles were evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 (50 ml) and 1N NaOH (20 ml). The organic layer was washed with water (30 ml) and brine (20 ml), dried ($MgSO_4$), concentrated, and purified by PTLC (2:98 MeOH/CH_2Cl_2) to give the product (71 mg, 55%). MS (ES) *m/e* 510 $(M+H)^+$.

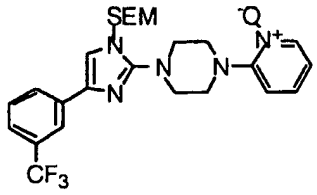
Step 2:

Reaction of the product of Step 1 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the product (52 mg, 99%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 7.81 (1H, m), 7.42 (2H, m), 7.20 (1H, d, *J*=3.6 Hz), 7.05 (1H, s), 6.62 (1H, d, *J*=3.6 Hz), 3.61 (4H, m), 3.51 (4H, m). MS (ES) *m/e* 380 $(M+H)^+$.

Example 28



Step 1:

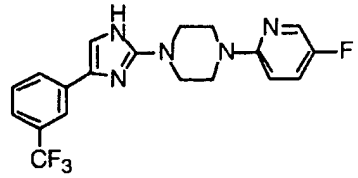


A solution of the product of Example 23, Step 2 (129 mg, 0.303 mmol), 2-chloropyridine N-oxide hydrochloride (77 mg, 0.46 mmol), and triethylamine (282 mg, 2.78 mmol) in EtOH (5 ml) was refluxed for 16 h. The volatiles were evaporated and the residue was partitioned between CH_2Cl_2 (40 ml) and water (20 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (6:94 MeOH/CH_2Cl_2) to give the product (40 mg, 25%). MS (ES) *m/e* 520 $(M+H)^+$.

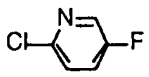
Step 2:

Reaction of the product of Step 1 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the product (28 mg, 94%). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.22 (1H, m), 7.95 (1H, s), 7.87 (1H, m), 7.4-7.6 (3H, m), 7.22 (2H, m), 7.13 (1H, m), 3.60 (4H, m), 3.55 (4H, m). MS (ES) *m/e* 390 $(M+H)^+$.

Example 29



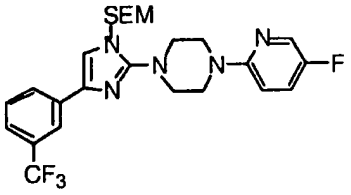
Step 1:



A stirred ice-cold solution of 2-chloro-5-aminopyridine (5.56 g, 43.2 mmol) in EtOH (50 ml) was treated with 50% aqueous HBF_4 (16 ml, 90 mmol). The mixture was cooled to –5°C and isoamyl nitrite (6.1 ml, 45 mmol) was added dropwise over 5 min. The mixture was stirred for another 30 min. at –5°C and then filtered. The filtercake was washed with

absolute EtOH and ether to give a pale yellow solid (6.77 g). The solid in dry heptane (35 ml) was gently refluxed for 3 h. Upon cooling to R.T. the upper layer was decanted, and the residue was stirred with ether (60 ml). After ether was evaporated at 10°C under reduced pressure, the residue was stirred with concentrated sulfuric acid (1 ml) for 16 h. The supernatant layer was decanted and the lower layer was rinsed with pentane (3x4 ml). Ice was added, followed by 5N NaOH (8 ml). The mixture was extracted with ether (50 ml, then 2x20 ml), dried ($MgSO_4$), and concentrated to give the product (1.5 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, d, *J*=3.2 Hz), 7.40 (1H, m), 7.32 (1H, dd, *J*=3.6, 8.8 Hz).

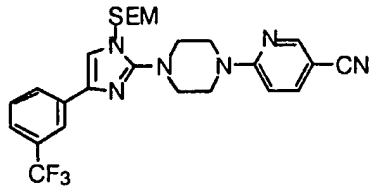
Step 2:



29-2-1

A mixture of the product of Example 23, Step 2 (97 mg, 0.23 mmol), the product of Step 1 (45 mg, 0.34 mmol), palladium(II) acetate (6 mg, 0.03 mmol), 2-(di-*t*-butylphosphino)biphenyl (7 mg, 0.02 mmol), and sodium *t*-butoxide (69 mg, 0.72 mmol) in toluene (2 ml) was heated to 100°C in a sealed vessel for 3 h. The mixture was diluted with CH_2Cl_2 (40 ml) and filtered. The filtrate was evaporated to dryness and purified by PTLC (2:98 MeOH/CH_2Cl_2) to give the product (60 mg, 50%). MS (ES) *m/e* 522 $(M+H)^+$.

Coupling of the product of Example 23, Step 2 with 2-chloropyridine-5-carbonitrile by essentially the same procedure gave:

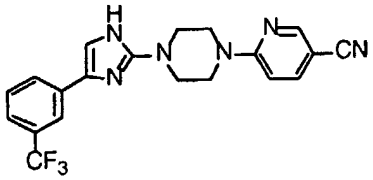


29-2-2

Step 3:

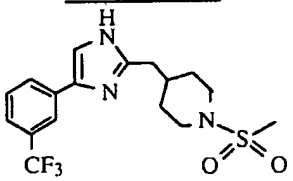
A solution of 29-2-1 (59 mg, 0.11 mmol) in MeOH (2 ml) and 5N HCl (5 ml) was refluxed for 3 h. The reaction mixture was partitioned between CH_2Cl_2 (50 ml) and aq. NH_4OH (25 ml). The organic layer was dried ($MgSO_4$), concentrated, and purified by PTLC (4:96 MeOH/CH_2Cl_2) to give the product (38 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, d, *J*=3.2 Hz), 7.89 (1H, m), 7.81 (1H, m), 7.41 (2H, m), 7.26 (1H, m), 7.05 (1H, s), 6.66 (1H, dd, *J*=3.6, 9.2 Hz), 3.58 (4H, m), 3.48 (4H, m). MS (ES) *m/e* 392 $(M+H)^+$.

Reaction of 29-2-2 with HCl/MeOH by the procedure of Example 5, Step 4 afforded the following compounds:

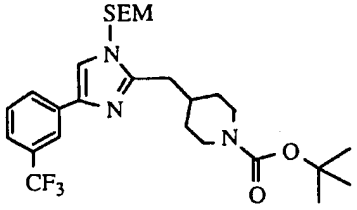


29A MS (ES) *m/e* 399 $(M+H)^+$.

Example 30



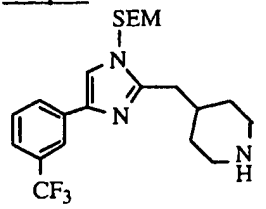
Step 1:



To an ice-cold solution of N-t-butoxycarbonyl-4-methylene-piperidine (Tetrahedron Letters, 37 (1996), 5233) (151 mg, 0.77 mmol) in THF (3 ml) was slowly added 9-BBN (0.5N in THF; 1.5 ml, 5.7 mmol). After 5 min. the cold bath was removed and stirring was continued at R.T. for 3 h to give solution A. Preparation 2 (350 mg, 0.75 mmol), $CsCO_3$ (299 mg, 0.92 mmol), triphenylarsine (24 mg, 0.08 mmol), and Pd(dppf)Cl_2 (24 mg, 0.03 mmol) in DMF (5 ml) and water (0.2 ml) was

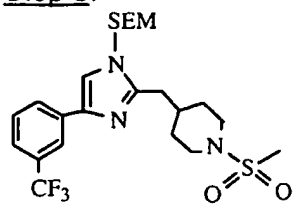
purged with N_2, and solution A was added via cannula. The reaction mixture was stirred overnight, then poured into ice-water and extracted with EtOAc (50 ml). The aqueous layer was basified to pH 10-11 and extracted with EtOAc (50 ml). The combined EtOAc layers were dried ($MgSO_4$), filtered and evaporated. Purification of the residue by PTLC (1:99 2 M NH_3 in CH_3OH /CH_2Cl_2) gave the product (177 mg, 49%). ^1H NMR (400 MHz, CD_3OD): δ 8.03 (s, 1H), 7.94 (d, 1H, *J*=8 Hz), 7.65 (s, 1H), 7.53 (m, 2H), 5.35 (s, 2H), 4.06 (m, 2H), 3.62 (t, 2H, *J*=8.2 Hz), 2.77 (m, 4H), 2.07 (m, 1H), 1.67 (m, 2H), 1.42 (s, 9H), 1.22 (m, 2H), 0.93 (t, 2H, *J*=8.2 Hz), -0.02 (s, 9H).

Step 2:



A solution of the product of Step 1 (558 mg, 1.18 mmol) in TFA (1.25 ml) and CH_2Cl_2 (10 ml) was stirred in an ice bath for 5 min., then at R.T. for 45 min. The reaction mixture was cooled in ice, then 1 N NaOH (20 ml) and CH_2Cl_2 (30 ml) was added. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by PTLC (6:94 2 M NH_3 in CH_3OH/CH_2Cl_2) to give the product (215 mg, 42%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.93 (m, 1H), 7.46 (m, 2H), 7.25 (s, 1H), 5.22 (s, 2H), 3.51 (t, 2H, *J*=8.2 Hz), 3.09 (m, 2H), 2.70 (m, 2H), 2.62 (m, 2H), 2.04 (m, 1H), 1.93 (bs, 1H), 1.75 (m, 2H), 1.27 (m, 2H), 0.93 (t, 2H, *J*=8.6 Hz), -0.02 (s, 9H).

Step 3:



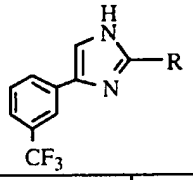
Reaction of the product of Step 2 (51 mg, 0.12 mmol) with CH_3SO_2Cl by the procedure of Example 5, Step 3, gave the product (55 mg, 100%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.91 (m, 1H), 7.46 (m, 2H), 7.25 (s, 1H), 5.23 (s, 2H), 3.81 (m, 2H), 3.54 (t, 2H, *J*=8.6

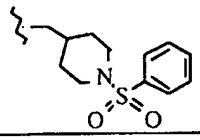
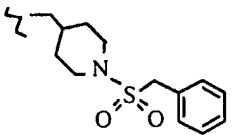
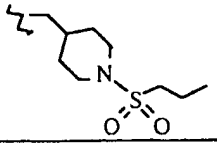
Hz), 2.77 (s, 3H), 2.70 (m, 4H), 2.15 (m, 1H), 1.89 (m, 2H), 1.45 (m, 2H), 0.92 (t, 2H, *J*=8.6 Hz), -0.02 (s, 9H).

Step 4:

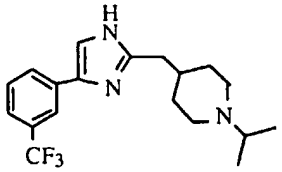
Using the procedure of Example 2, Step 4, reaction of the product of Step 3 (55 mg, 0.12 mmol) with HCl/CH_3OH afforded the product (38 mg, 100%). ^1H NMR (400 MHz, CD_3OD): δ 8.00 (s, 1H), 7.91 (d, *J*=7.2 Hz, 1H), 7.50 (m, 3H), 3.70 (m, 2H), 2.79 (s, 3H), 2.71 (m, 4H), 1.90 (m, 1H), 1.77 (m, 2H), 1.37 (m, 2H). MS (FAB) *m/e* 388 $(M+H)^+$.

Using appropriate starting materials and essentially the same procedure, the following compounds were prepared:

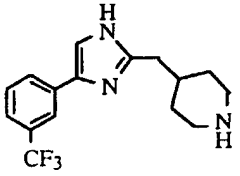


Ex.	R	Data
30A		MS (CI) *m/e* 450 $(M+H)^+$
30B		MS (CI) *m/e* 464 $(M+H)^+$
30C		MS (FAB) *m/e* 416 $(M+H)^+$

Example 31



Step 1:

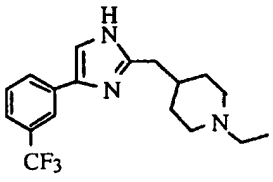


Using the procedure of Example 2, Step 4, reaction of the product of Example 30, Step 2 (177 mg, 0.40 mmol) with 5M HCl/CH_3OH afforded the product (74 mg, 60%). MS (CI) *m/e* 310 $(M+H)^+$.

Step 2:

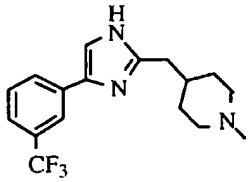
Using a procedure analogous to Example 4, Step 2, reductive alkylation of the product of Step 1 (33 mg, 0.11 mmol) with acetone gave the product (25 mg, 65%). ^1H NMR (400 MHz, CD_3OD): δ 7.99 (s, 1H), 7.91 (d, 1H, *J*=7.6 Hz), 7.51 (m, 2H), 7.43 (s, 1H), 2.91 (m, 2H), 2.69 (m, 3H), 2.20 (m, 2H), 1.79 (m, 1H), 1.70 (m, 2H), 1.35 (m, 2H), 1.06 (d, 6H, *J*=6.6 Hz). MS (CI) *m/e* 352 $(M+H)^+$.

Using appropriate starting materials and procedures, the following compounds were prepared:



31A

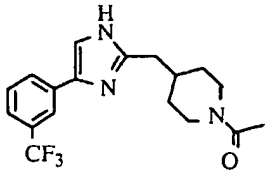
MS (CI) *m/e* 338 $(M+H)^+$



31B

MS (FAB) *m/e* 324 $(M+H)^+$

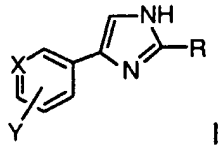
Example 32



A solution of Example 31, Step 1 (27 mg, 0.087 mmol), acetic anhydride (15 μL, 0.16 mmol), Et_3N (45 μL, 0.32 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 ml) was stirred at R.T. overnight. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with sat'd NH_4Cl (20 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by PTLC (5:95 CH_3OH/CH_2Cl_2) to give the product (14 mg, 46%). ^1H NMR (400 MHz, CD_3OD): δ 8.00 (s, 1H), 7.93 (m, 1H), 7.65-7.50 (m, 3H), 4.51 (m, 1H), 3.92 (m, 1H), 3.10 (m, 1H), 2.74 (m, 1H), 2.63 (m, 1H), 2.08 (s, 3H), 2.04 (m, 1H), 1.73 (m, 2H), 1.35-1.10 (m, 3H). MS (FAB) *m/e* 352 $(M+H)^+$.

What is Claimed is:

1. A compound having the structural formula



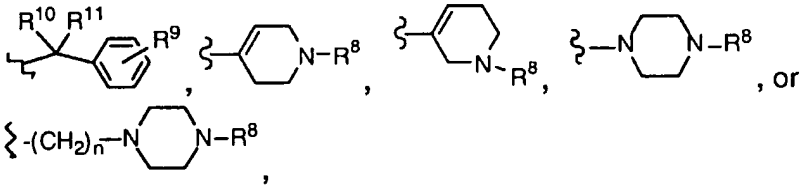
I

or a pharmaceutically acceptable salt, solvate or N-oxide thereof, wherein

X is =CH- or =N-;

Y is 1 to 3 substituents independently selected from the group consisting of H, halogen, trihaloalkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_7-cycloalkyl, C_1-C_6 alkyl substituted by C_3-C_7-cycloalkyl,-OH, -O(C_1-C_6)alkyl, -SH, -S(C_1-C_6)alkyl, or –CN.

R is R^1-phenyl, R^1-pyridyl, adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6alkyl, C_3-C_7-cycloalkyl, or heterocycloalkyl selected from the group consisting of 4 to 6 membered rings comprising 3 to 5 carbon ring members and 1 to 3 ring members selected from the group consisting of –NR^8-, -O- and -S-, heterocycloalkyl(C_1-C_6)alkyl wherein heterocycloalkyl is as defined above, heteroaryl(C_1-C_6)alkyl,



provided that when R is R^1-phenyl, R^1-pyridyl, adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6alkyl, or C_3-C_7-cycloalkyl, Y is 3-CF_3;

n is 0, 1, 2 or 3;

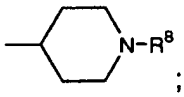
R^1 is 1-3 substituents independently selected from the group consisting of hydroxy(C_1-C_6)alkyl; NO_2; -CHO, -C(O)O(C_1-C_6)alkyl; -C(O)NR^4R^5; -$(CH_2)_p NR^4R^5$; -$(CH_2)_p NR^4R^6$; -$NR^4SO_2R^7$; -NHCOH; -NR^4COR^5; -NHC(O)NR^4R^5; aryl; and heteroaryl;

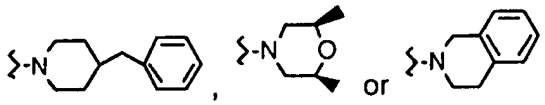
p is 0, 1, 2 or 3;

R^4 is hydrogen or C_1-C_6 alkyl;

R^5 is C_1-C_6 alkyl, aryl or heteroaryl; provided R^4 and R^5 are not both C_1-C_6 alkyl, and provided that when R^4 is hydrogen, R^5 is not C_1-C_6

alkyl; or R^4 and R^5 together are C_3-C_6 alkylene and together with the nitrogen to which they are attached form a 4-7 membered ring; or R^4 and R^5, together with the nitrogen to which they are attached, form a 5, 6 or 7-membered ring, wherein 1 or 2 ring members are independently selected from the group consisting of -O-, -S- and $-NR^{12}$-;

R^6 is C_3-C_7 cycloalkyl, benzyl, diphenylmethyl or  ; or R^4 and R^6, together with the nitrogen to which they are attached form a group of the formula



R^7 is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, benzyl, aryl, or heteroaryl;

R^8 is hydrogen, C_1-C_6 alkyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_3-C_7 cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, $-SO_2$-R^7, aryl, heteroaryl, -$CONR^4R^5$ or -C(O)-O-(C_1-C_6)alkyl;

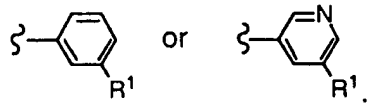
R^9 is 1 to 3 substituents independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogeno and $-CF_3$;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{10} and R^{11}, together with the carbon to which they are attached, form a C_3-C_7 ring; and

R^{12} is hydrogen, C_1-C_6 alkyl, -C(O)-(C_1-C_6 alkyl), $-SO_2$-R^7, R^9-phenyl, -$CONR^4R^5$, -C(O)-O-(C_1-C_6)alkyl, -CHO, C_3-C_7 cycloalkyl, (C_3-C_7)cycloalkyl(C_1-C_6)alkyl, benzyl, benzoyl, -C(O)(C_3-C_7)cycloalkyl, -C(O)(C_1-C_6)alkylphenyl, pyridylmethyl, -C(O)pyridyl, -C(O)N(di-(C_1-C_6)-alkyl) or 4-tetrahydropyranyl.

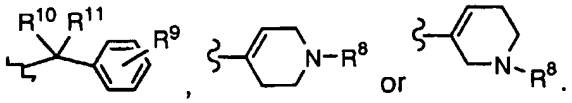
2. The compound of claim 1 wherein R is R^1-phenyl or R^1-pyridyl.

3. The compound of claim 2 wherein R is

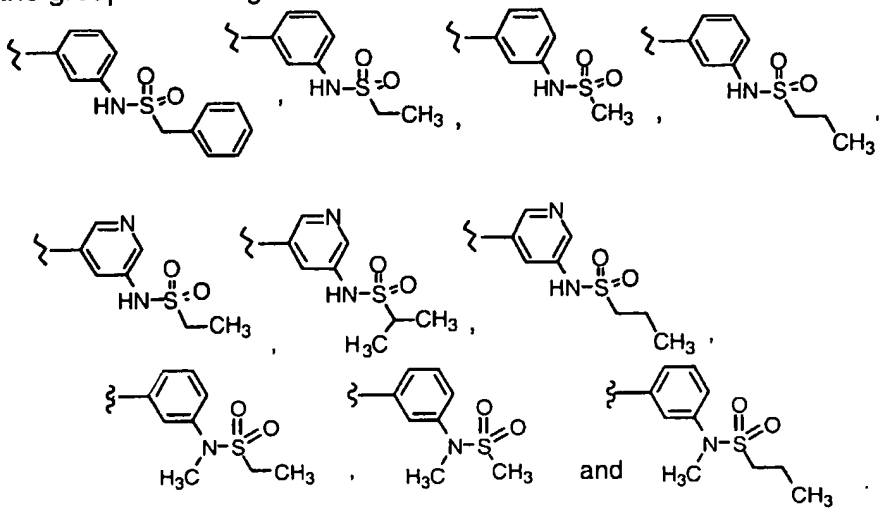


4. The compound of claim 3 wherein R^1 is $-NR^4SO_2R^7$, R^4 is H or C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl.

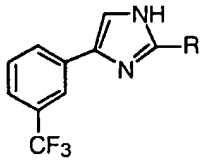
5. The compound of claim 1 wherein R is adamantyl, -$(CH_2)_n$-O-(R^9-phenyl), -$(CH_2)_n$-S-(R^9-phenyl), -CF_3, C_1-C_6 alkyl, C_3-C_7-cycloalkyl, heterocycloalkyl, heterocycloalkyl-(C_1-C_6)alkyl, heteroaryl-(C_1-C_6)alkyl,



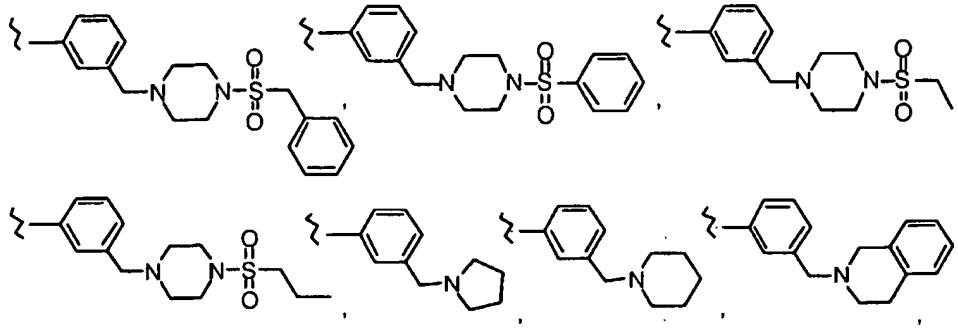
6. The compound of claim 1 wherein X is =CH- and R is selected from the group consisting of:

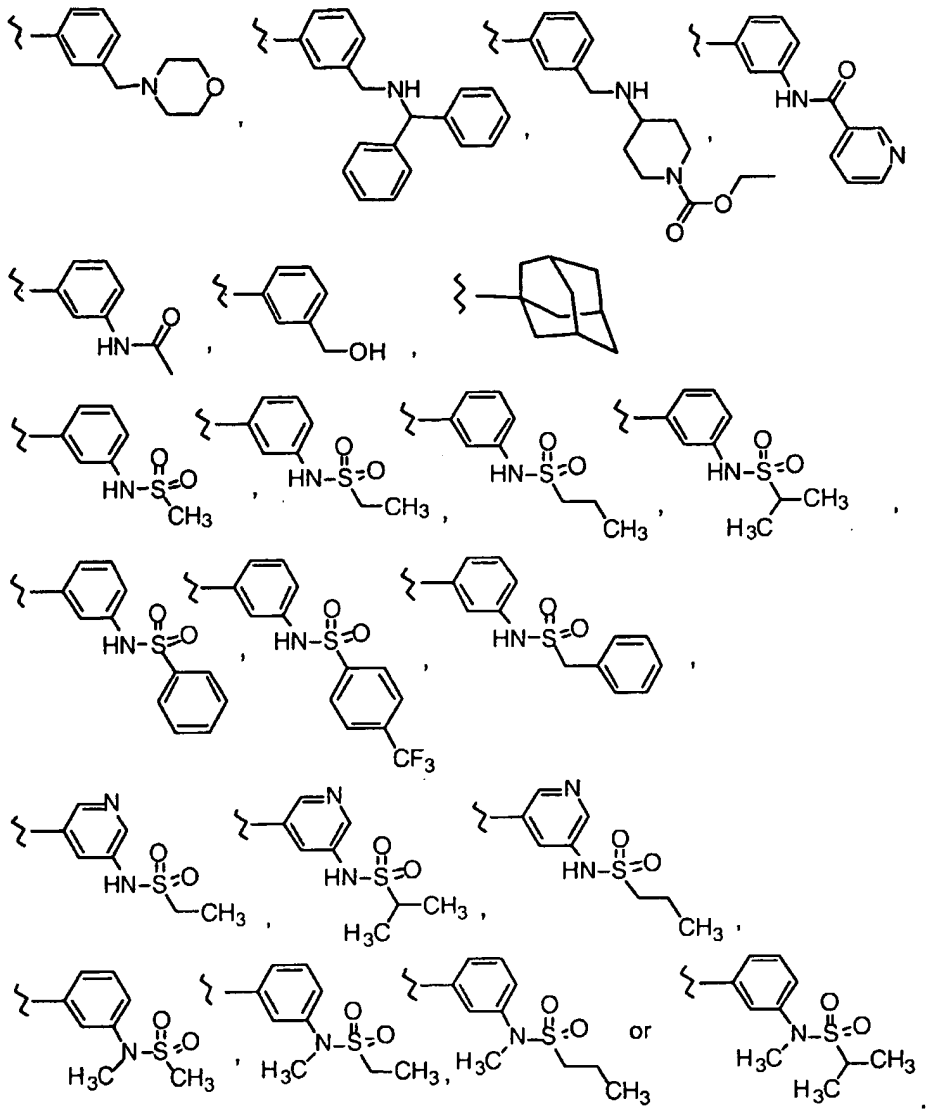


7. The compound of claim 1 selected from the group consisting of compounds of the formula

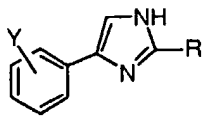


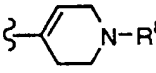
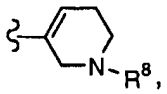
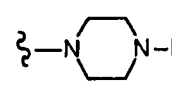
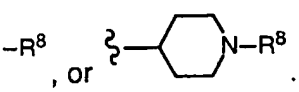
wherein R is





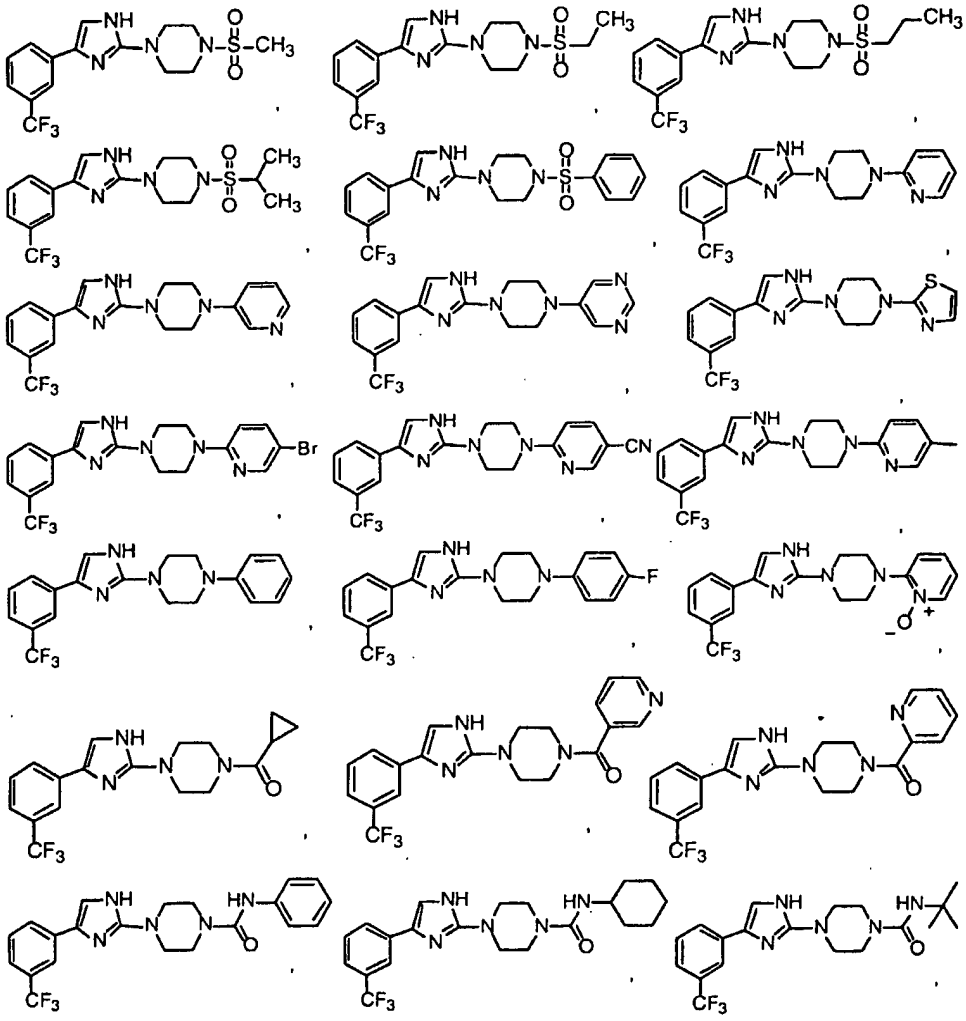
8. The compound of claim 1 selected from the group consisting of compounds of the formula

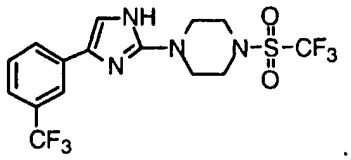


wherein Y is 1 – 3 substituents selected from the group consisting of H, halogen, trihaloalkyl, or C_1-C_6 alkyl, and wherein R is  ,  ,  , or  .

9. The compound of claim 8 wherein R^8 is C(O)-(C_1-C_6 alkyl), -C(O)-(C_3-C_7 cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, -SO_2-R^7, aryl, heteroaryl, or -$CONR^4R^5$.

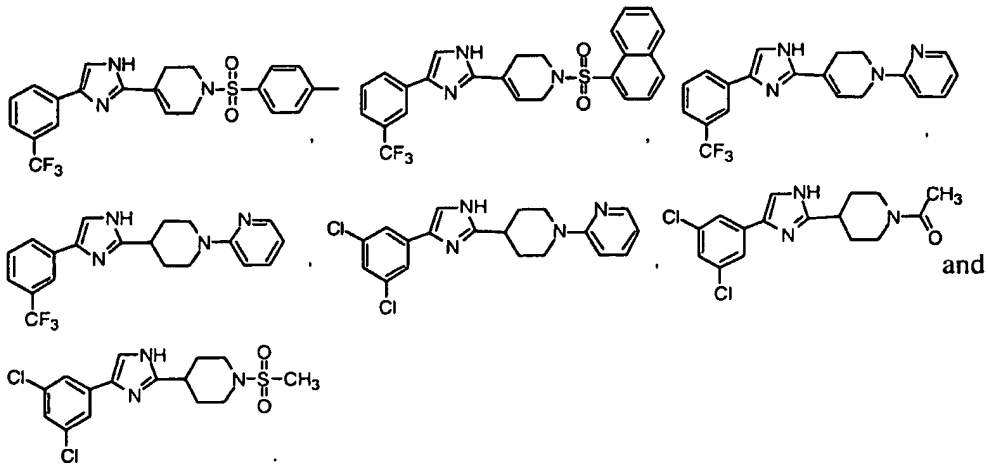
10. The compound of claim 1 selected from the group consisting of





and

11. The compound of claim 1 selected from the group consisting of



and

12. A pharmaceutical composition comprising a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

13. The use of a compound of claim 1 for the manufacture of a medicament for use in the treatment of eating disorders or diabetes in a patient in need of such treatment.

14. A pharmaceutical composition comprising a compound as defined in claim 11 in combination with a pharmaceutically acceptable carrier.

15. The use of a compound of claim 11 for the manufacture of a medicament for use in the treatment of eating disorders or diabetes in a patient in need of such treatment.

16. The compound of claim 1 for use in the treatment of eating disorders or diabetes in a patient in need of such treatment.

17. The compound of claim 11 for use in the treatment of eating disorders or diabetes in a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/33832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/54 C07D413/10 C07D401/10 C07D401/04 C07D401/12
C07D403/12 C07D401/06 A61K31/415 //(C07D413/10,265:00,
233:00),(C07D401/10,233:00,217:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 01128 A (NEUROGEN CORP ;PFIZER (US)) 14 January 1999 (1999-01-14) cited in the application the whole document	1-17
Y	WO 99 48873 A (SQUIBB BRISTOL MYERS CO) 30 September 1999 (1999-09-30) the whole document	1-17
A	WO 98 24785 A (KATO MASAYUKI ;NODA YUKA (JP); SPEARS GLEN W (JP); HARADA KEIKO (J) 11 June 1998 (1998-06-11) page 1; examples 4,18,19.32	1-17
A,P	WO 00 64880 A (DESAI MAHESH N ;NOBLE STEWART A (US); WONG WAI C (US); MARZABADI M) 2 November 2000 (2000-11-02) abstract; claims 16-18,52-55	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2001	21/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/US 00/33832

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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